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External Review Draft. Volume 5

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Volume V of V

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LIST OF ABBREVIATIONS (continued)

max $\dot{V}_E$	Maximum ventilation
max $\dot{V}O_2$	Maximal aerobic capacity
MBC	Maximum breathing capacity
MEFR	Maximum expiratory flow rate
MEFV	Maximum expiratory flow-volume curve
MetHb	Methemoglobin
MMAD	Mass median aerodynamic diameter
MMFR or MMEF	Maximum mid-expiratory flow rate
MVV	Maximum voluntary ventilation
NBKI	Neutral buffered potassium iodide
$(NH_4)_2SO_4$	Ammonium sulfate
NO_2	Nitrogen dioxide
ΔN_2, dN_2	Nitrogen washout
O_2	Oxygen
O_2-	Oxygen radical
O_3	Ozone
$P(A-a)O_2$	Alveolar-arterial oxygen pressure difference
PABA	para-aminobenzoic acid
P_ACO_2	Alveolar partial pressure of carbon dioxide
$PaCO_2$	Arterial partial pressure of carbon dioxide
PAN	Peroxyacetyl nitrate
P_AO_2	Alveolar partial pressure of oxygen
PaO_2	Arterial partial pressure of oxygen
PBZN	Peroxybenzoyl nitrate
PEF	Peak expiratory flow
PEFV	Partial expiratory flow-volume curve
PG	Prostaglandin
pH_a	Arterial pH
P_L	Transpulmonary pressure
PMN	Polymorphonuclear leukocyte
P_{st}	Static transpulmonary pressure
PUFA	Polyunsaturated fatty acid
R	Resistance to flow
Raw	Airway resistance

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Data on health and welfare effects are emphasized, but additional information is provided for understanding the nature of the oxidant pollution problem and for evaluating the reliability of effects data as well as their relevance to potential exposures to ozone and other photochemical oxidants at concentrations occurring in ambient air. Separate chapters are presented on the following exposure-related topics pertaining to ozone and other photochemical oxidants: properties, chemistry, and measurement; concentrations typically found in ambient air; formation and transport once formed; and nature, source, measurement, and concentrations of precursors.

The specific areas addressed by chapters on health and welfare effects are: the toxicological appraisal of effects of ozone and other oxidants; effects observed in controlled, human exposures; effects observed in field and epidemiological studies; effects on vegetation seen in field and controlled exposures; effects on natural and agroecosystems; and effects on nonbiological materials observed in field and chamber studies.

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
AM	Alveolar macrophage
ANOVA	Analysis of variance
AOD	Airway obstructive disease
ATPS	ATPS condition (ambient temperature and pressure, saturated with water vapor)
BTPS	BTPS conditions (body temperature, barometric pressure, and saturated with water vapor)
CC	Closing capacity
C_{dyn}	Dynamic lung compliance
CE	Continuous exercise
CHEM	Gas phase chemiluminescence
CHESS	Community Health Environmental Surveillance System
C_L	Lung compliance
C_{Lst}	Static lung compliance
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COLD	Chronic obstructive lung disease
COPD	Chronic obstructive pulmonary disease
CO_2	Carbon dioxide
CV	Closing volume
D_L	Diffusing capacity of the lungs
D_{LCO}	Carbon monoxide diffusion capacity of the lungs
E	Elastance
ECG, EKG	Electrocardiogram
EEG	Electroencephalogram
EPA	U.S. Environmental Protection Agency
ERV	Expiratory reserve volume
FEF_{max}	The maximal forced expiratory flow achieved during an FVC.
FEF	Forced expiratory flow

LIST OF ABBREVIATIONS (continued)

$FEF_{200-1200}$	Mean forced expiratory flow between 200 ml and 1200 ml of the FVC [formerly called the maximum expiratory flow rate (MEFR)].
$FEF_{25-75\%}$	Mean forced expiratory flow during the middle half of the FVC [formerly called the maximum mid-expiratory flow rate (MMFR)].
$FEF_{75\%}$	Instantaneous forced expiratory flow after 75% of the FVC has been exhaled.
FEV	Forced expiratory volume
FEV_1	Forced expiratory volume in 1 sec
FEV_t/FVC	A ratio of timed forced expiratory volume (FEV_t) to forced vital capacity (FVC)
FIVC	Forced inspiratory vital capacity
f_R	Respiratory frequency
FRC	Functional residual capacity
FVC	Forced vital capacity
G	Conductance
G-6-PD	Glucose-6-phosphate dehydrogenase
Gaw	Airway conductance
GS-CHEM	Gas-solid chemiluminescence
GSH	Glutathione
Hb	Hemoglobin
Hct	Hematocrit
HO·	Hydroxy radical
H_2O	Water
IC	Inspiratory capacity
IE	Intermittent exercise
IRV	Inspiratory reserve volume
IVC	Inspiratory vital capacity
LDH	Lactate deyhydrogenase
LD_{50}	Lethal dose (50 percent)
LM	Light microscopy
MAST	KI-coulometric (Mast meter)

LIST OF ABBREVIATIONS (continued)

RBC	Red blood cell
R_{coll}	Collateral resistance
rh	Relative humidity
R_L	Total pulmonary resistance
RQ, R	Respiratory quotient
R_t	Total respiratory resistance
R_{ti}	Tissue resistance
RV	Residual volume
SaO_2	Arterial oxygen saturation
SBNT	Single-breath nitrogen test
SCE	Sister chromatid exchange
Se	Selenium
SEM	Scanning electron microscopy
SGaw	Specific airway conductance
SH	Sulfhydryls
SOD	Superoxide dismutase
SO_2	Sulfur dioxide
SO_4	Sulfate
SPF	Specific pathogen-free
SRaw	Specific airway resistance
STPD	STPD conditions (standard temperature and pressure, dry)
TEM	Transmission electron microscopy
TGV	Thoracic gas volume
THC	Total hydrocarbons
TLC	Total lung capacity
TV	Tidal volume
UV	Ultraviolet photometry
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_A/\dot{Q}$	Ventilation/perfusion ratio
VC	Vital capacity
$\dot{V}CO_2$	Carbon dioxide production
V_D	Physiological dead space

LIST OF ABBREVIATIONS (continued)

$\dot{V}_D$	Dead-space ventilation
$V_{D\ anat}$	Anatomical dead space
$\dot{V}_E$	Minute ventilation; expired volume per minute
$\dot{V}_I$	Inspired volume per minute
V_L	Lung volume
$\dot{V}_{max}$	Maximum expiratory flow
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_2$, $\dot{Q}O_2$	Oxygen consumption

MEASUREMENT ABBREVIATIONS

g	gram
hr/day	hours per day
kg	kilogram
kgm/min	kilogram-meter/min
L/min	liters/min
L/s	liters/sec
ppm	parts per million
mg/kg	milligrams per kilogram
mg/m^3	milligrams per cubic meter
min	minute
ml	milliliter
mm	millimeter
$\mu g/m^3$	micrograms per cubic meter
μm	micrometers
μM	micromole
sec	second

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Chapter 13: Evaluation of Integrated Health Effects Data for Ozone and Other Photochemical Oxidants

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11. CONTROLLED HUMAN STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

11.1 INTRODUCTION

Four major summaries on the effects of controlled human exposure to ozone (O_3) have been published (National Research Council, 1977; U.S. Environmental Protection Agency, 1978; World Health Organization, 1978; and Hughes, 1979). In addition, two other reports (National Air Pollution Control Administration, 1970; F.R. April 30, 1971) have reviewed earlier studies.

In 1977 the National Research Council report on ozone and other photochemical oxidants stated a need for comprehensive human experimental studies that were carefully controlled and documented to ensure reproducibility. This statement was understandable, considering that the major portion of the report's section on controlled human studies was devoted to reviews of test methods, protocol designs, review of a scant amount of published data, and recommendations for future studies. The available data on controlled studies through 1975 were limited to some 20 publications. Nonetheless, this data base represented a substantial increase above the information available prior to 1970, and it became evident that exposure to O_3 at low ambient concentrations resulted in some degree of pulmonary dysfunction. Additional research was conducted in the intervening years, and by 1978 data were available from studies conducted on over 200 individuals (Table 11-1). By this time the first reports were available indicating that under the same exposure conditions, greater functional deficits were measured during exercise than at rest. In addition, five studies in which several pollutants (nitrogen dioxide, sulfur dioxide, and carbon monoxide plus oxidants) were present during exposure became available for review. Two reports on repeated daily exposure to O_3 ("adaptation") had appeared, as well as one experimental study in which asthmatics were evaluated. This research was just the beginning of interest in O_3 as an ambient pollutant affecting pulmonary functions of exposed man. Although the data base was still smaller than desirable, a general conception of this particular air pollutant's influence was beginning to form.

The early reports summarized in Table 11-1 were described in detail in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978). In this chapter, emphasis has been placed on the more recent literature; however, some of the older studies have been reviewed again. Tables

TABLE 11-1. HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978[a]

Ozone concentration		Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
$\mu g/m^3$	ppm					
196	0.10	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	$P(A-a)O_2$ and R_{aw} increased.	12 male	von Nieding et al., 1977
196 784 1176 1960	0.1 0.4 0.6 1.0	I	1 hr R	Airway resistance: mean increases of 3.3% (0.1 ppm), 3.5% (0.4 ppm), 5.8% (0.6 ppm), and 19.3% (1.0 ppm) at 0 hr after exposure; mean increases of 12.5% (0.4 ppm), 5% (0.6 and 1.0 ppm) at 1 hr after exposure; one subject had history of asthma and experienced hemoptysis 2 days after 1 ppm. No symptoms at 0.1 ppm; odor detected at 0.4 and 0.6 ppm; throat irritation and cough at 1.0 ppm.	4 male	Goldsmith and Nadel, 1969
294 588	0.15 0.30	UV, NBKI	1 hr (mouthpiece) R (11) & CE (29, 43, 66)	RV, $FEV_{1.0}$, MMFR, and V_T decreased and f_B increased at 0.30 ppm during IE (66); small but nonsignificant changes at 0.15 ppm. Congestion, wheezing, and headache reported.	6 male	DeLucia and Adams, 1977
392 980	0.2 0.5	I	3 hr/day 6 days/week x 12 weeks	Slight (nonsignificant) decrease in VC and significant decrease in $FEV_{1.0}$ at 0.5 ppm toward end of 12 weeks; returned to normal within 6 weeks after exposure; 0.66 (0.2 ppm), 0.80 (0.5 ppm) upper respiratory infections/person in 12 weeks compared to 0.95 for the controls. No irritating symptoms, but could detect ozone by smell at 0.5 ppm.	6 male	Bennett, 1962
451	0.23	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in spirometry, closing volume, and N_2 washout; small blood biochemical changes; increased frequency of symptoms reported. Medication maintained during exposure.	20 male (asthma) 2 female (asthma)	Linn et al., 1978
490 725 980	0.25 0.37 0.50	CHEM, NBKI	2-4 hr R & IE (2xR) @ 15-min intervals	No effect in normal reactors. Changes (2-12%) observed in spirometry, lung mechanics, and small airway function in non-reactors (IE) and hyperreactors (R) at 0.5 ppm.	16 normal and reactive subjects	Hackney et al., 1975a,b,c

TABLE 11-1. HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978[a] (continued)

Ozone concentration		Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
$\mu g/m^3$	ppm					
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in spirometry or small airway function in the combined group; sensitive subjects had decreased $FEV_{1.0}$ (4.7%).	4 normal (L.A.) 4 sensitive (L.A.)	Bell et al., 1977
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in group mean pulmonary function; individual subjective symptoms and spirometric decrements were more severe in Toronto than L.A. subjects. Blood enzyme activity increased in both groups, but RBC fragility increased in Toronto subjects only.	2 male (Toronto) 2 female (Toronto) 3 male (L.A.) 1 female (L.A.)	Hackney et al., 1977b
725 1470	0.37 0.75	MAST, NBKI	2 hr IE (2xR) @ 15-min intervals	At 0.37 ppm, less than 20% decrements in spirometry. Smokers less responsive than nonsmokers. At 0.75 ppm, severe decrements in spirometric variables (20%-55%). Smokers more responsive, with RV and CC increased.	12 male	Bates and Hazucha, 1973 Hazucha et al., 1973 Hazucha, 1973
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr R (11) & IE (29) @ 15-min intervals	0.75 ppm: at rest, less than 21% decrements in spirometry, while during IE nearly 33% decrements in spirometry and dN_2. Relatively smaller effects at lower concentrations. Reasonably good correlation between dose (conc. x min. vent.) and changes in spirometric variables.	20 male 8 female (divided into 6 exposure groups)	Silverman et al., 1976
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr R (11) & IE (29) @ 15-min intervals	f_B increased and V_T decreased with exercise; $\dot{V}O_2$ not affected by exposure. Variables correlated to total dose of ozone.	20 male 8 female (divided into 6 exposure groups)	Folinsbee et al., 1975
784	0.4	CHEM, NBKI	1-4 hr IE (4xR) for two 15-min periods	FVC and MMEF decreased and R_{aw} increased at 2 hr and 4 hr; $FEV_{1.0}$, $\dot{V}_{50}$, and $\dot{V}_{25}$ decreased at 4 hr only.	22 male	Knelson et al., 1976
784	0.4	CHEM, NBKI	2.25 hr IE (2xR) @ 15-min intervals	FVC, $FEV_{1.0}$, and MMF decreased in new arrivals, which were more responsive than L.A. residents. Inconsistent changes in blood biochemistry.	6 female (L.A.) 7 female (new arrival) 2 male (new arrival)	Hackney et al., 1976
980	0.5	CHEM, NBKI	4 days 2.5 hr/day IE (2xR) @ 15-min intervals	Very small changes in pulmonary function; temporal pattern of these changes is suggestive of "adaptation."	6 male (atopic)	Hackney et al., 1977a

TABLE 11-1. HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978[a] (continued)

Ozone concentration μg/m³	Ozone concentration ppm	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
980	0.5	CHEM, NBKI	2 hr R (9) & IE (37) for 30 min	Changes in pulmonary function (FVC, $FEV_{1.0}$, FEF_{25-75}) were greatest immediately following exercise. Heat stress potentiated the response while relative humidity had insignificant effects.	14 male (divided into 2 exposure groups)	Folinsbee et al., 1977b
980	0.5	MAST, NBKI	6 hr IE (44) for two 15-min periods	FVC, $FEV_{3.0}$, and SG_{aw} decreased and R_L increased. Nonsmokers were more susceptible. Inconsistent changes in lung mechanics and small airway function.	19 male 1 female (equally divided by smoking history)	Kerr et al., 1975
1176	0.6	CHEM, NBKI	2 hr (noseclips) R	Bronchoreactivity to histamine increased following exposure; persisted for up to 3 weeks; blocked by atropine.	3 male 5 female	Golden et al., 1978
1176	0.6	CHEM, NBKI	2 hr IE for two 15-min periods	Significant decrements in spirometric variables (19%-35%). Cough and pain on deep inspiration most frequently reported; no symptoms persisted beyond 48 hr.	20 male	Ketcham et al., 1977
1176 1568	0.6 0.8	MAST	2 hr R(9)	DL_{CO}: mean decrease of 25% (11/11 subjects). VC: mean decrease of 10% (10/10 subjects). $FEV_{0.75}$ x 40: mean decrease of 10%. FEF 25-75: mean decrease of 15%, which was not significant. Mixing efficiency: no change (2/2 subjects). Airway resistance: slight increase, but within normal limits. Dynamic compliance: no change (2/2 subjects). Substernal soreness and tracheal irritation 6 to 12 hr after exposure.	10 male 1 female	Young et al., 1964
1470	0.75	MAST, NBKI	2 hr IE @ 15-min intervals	HR_{max}, $\dot{V}_E$, V_T, $\dot{V}O_{2max}$, and maximum workload all decreased. At maximum workload only, f_B decreased (45%) and V_T increased (29%).	13 male	Folinsbee et al., 1977a
1470	0.75	MAST, NBKI	2 hr R & IE (2XR) @ 15-min intervals	FEF_{50} and P_{ST}TLC decreased, R_L increased; returned to control levels within 24 hr. IE attenuated changes in R_L, C_{dyn}, maxP_{tp}, and spirometry. Cough and substernal soreness reported.	13 male: 10(R) & 3(IE)	Bates et al., 1972

TABLE 11-1. HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978[a] (continued)

Ozone concentration		Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
µg/m³	ppm					
1764	0.9	MAST, NBKI	5 min CE	SG_{aw} decreased during and 5 min following exposure. Recovery complete within 30 min post-exposure.	4 male	Kagawa and Toyama, 1975
2940 3920	1.5 2.0	I	2 hr R	VC: decreased 13%; returned to normal in 22 hr. $FEV_{3.0}$: decreased 16.8% after 22 hr. Maximum breathing capacity decreased very slightly. CNS depression, lack of coordination, chest pain, tiredness for 2 weeks.	1 male	Griswold et al., 1957
Up to 7840	Up to 4.0	MAST	10-30 min R	VC: mean decrease of 16.5% (4/8 subjects showed decrease > 10%). $FEV_{1.0}$: mean decrease of 20% (5/8 subjects showed decrease > 10%. FEF_{25-75}: mean decrease of 10.5% (5/6 subjects showed a decrease). MBC: decrease of 12% (5/8 subjects showed decrease). DL_{CO}: decrease of 20 to 50% in 7/11 subjects; increase of 10 to 50% in 4/11 subjects; only 5/11 subjects tolerated 1 to 3 ppm for full 30 min. Wide variations in DL_{CO}. Headache, shortness of breath, lasting more than 1 hr.	11 subjects	Hallett, 1965
9800 19600	5-10	I	Not available	Drowsiness and headache reported.	3 male	Jordan and Carlson, 1913

[a] Cited in Air Quality Criteria for Ozone and Other Photochemical Oxidants, Research Triangle Park, NC: U.S. Environmental Protection Agency, EPA-600/87-004, April 1978.

[b] Measurement methods: MAST = KI-coulometric (Mast meter); I = iodometric; CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[c] Calibration methods: NBKI = neutral buffered potassium iodide.

[d] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or in multiples of resting ventilation.

[e] See Glossary for the definition of symbols.

have been provided to give the reader an overview of the studies discussed in the text and provide some additional information about measurement techniques and exposure protocols. Unless otherwise stated, the O_3 concentrations presented in the text and tables are the levels cited in the original manuscript. No attempt has been made to convert the concentrations to a common standard, although suggestions for conversion along with a discussion of O_3 measurement can be found in Chapter 5.

11.2 ACUTE PULMONARY EFFECTS OF OZONE

11.2.1 At-Rest Exposures

Results from studies reported prior to 1978 (Table 11-1) indicate that impairment of pulmonary function and pulmonary symptoms occur when normal subjects are exposed for 2 hr at rest to 1176-1568 $\mu g/m^3$ (0.6-0.8 ppm) of O_3 (Young et al., 1964), to 1479 $\mu g/m^3$ (0.75 ppm) of O_3 (Bates et al., 1972; Silverman et al., 1976), and to 980 $\mu g/m^3$ (0.5 ppm) of O_3 (Folinsbee et al., 1977b). In addition to decrements in the usual indicators of pulmonary function, Young et al. (1964) also found decreases in diffusion capacity of the lung (D_LCO).

Results from studies of at-rest exposures published since 1978 (Table 11-2) have generally confirmed these earlier findings. Folinsbee et al. (1978) observed decrements in forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), and other spirometric variables when 10 normal subjects rested for 2 hr while exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3; airway resistance (R_{aw}) was not affected. No changes in pulmonary function resulted from exposures to 588 or 196 $\mu g/m^3$ (0.3 or 0.1 ppm) of O_3. Horvath et al. (1979) reported that decreases in FVC and $FEV_{1.0}$ resulted from 2-hr at-rest exposures of 15 subjects (8 males, 7 females) to 980 and 1470 $\mu g/m^3$ (0.50 and 0.75 ppm) of O_3; the decreases at 0.75 ppm were greater than those at 0.50 ppm of O_3. No changes in pulmonary function were observed at 490 $\mu g/m^3$ (0.25 ppm) of O_3.

Kagawa and Tsuru (1979a) observed small decreases in specific airway conductance (SG_{aw}) when three subjects rested for 2 hr while exposed to 588 and 980 $\mu g/m^3$ (0.3 and 0.5 ppm) of O_3. In contrast to other studies, this is the only report of changes in airway resistance resulting from at rest exposures to O_3.

König et al. (1980) exposed 14 healthy nonsmokers (13 men, 1 woman) for 2 hr at rest to 0, 196, 627, and 1960 $\mu g/m^3$ (0.0, 0.10, 0.32, and 1.0 ppm) of O_3.

TABLE 11-2. STUDIES ON ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration $\mu g/m^3$	ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
196	0.1	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No effect on PaO_2 or R_{aw} taking into account intra-individual variation.	11 male	von Nieding et al., 1979
196 588 980	0.1 0.3 0.5	CHEM, NBKI	2 hr R (10), IE (31, 50, 67) @ 15-min intervals	Changes in pulmonary function found at 0.5 ppm during R and 0.3 and 0.5 ppm with IE. The magnitude of spirometric changes was generally related to ozone concentration and minute ventilation, but concentration showed stronger association. Effective dose-functional response curves developed.	40 male (divided into 4 exposure groups)	Folinsbee et al., 1978
196 627 1960	0.1 0.32 1.0	MAST, NBKI	2 hr R	No changes in SR_{aw} following exposure; SR_{aw} increased with ACH challenge at ≥0.32 ppm; SR_{aw} increased in 2/3 COLD patients at 0.1 ppm.	13 male 1 female (3 COLD) (1 asthma)	König et al., 1980
235 353 470 588 784	0.12 0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr IE (65) @ 15-min intervals	Small decreases in FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ at 0.12 and 0.18 ppm with larger decreases at ≥0.24 ppm; f and SR_{aw} increased and V_T decreased at ≥0.24 ppm; regression curves produced; coughing reported at all concentrations, pain and shortness of breath at ≥0.24 ppm.	135 male (divided into six exposure groups)	McDonnell et al., 1983
294 588	0.15 0.3	CHEM, NBKI	2 hr IE @ 15-min intervals	SG_{aw} and FVC decreased at 0.15 and 0.30 ppm O_3. Increased ΔN_2 at 0.15 ppm O_3. Questionable statistics.	15 male	Kagawa, 1983a
392	0.2	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	No meaningful changes in PAO_2, PaO_2, and $P(A-a)O_2$. Inconsistent changes in spirometric, plethysmographic, and ventilatory distribution variables.	13 male 5 female	Linn et al., 1979
392	0.2	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	Variable changes in $FEV_{1.0}$. Possible calibration error for spirometry.	9 reactive subjects; 4 (normal) 5 (asthma)	Linn et al., 1980

TABLE 11-2. STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978 (continued)

Ozone concentration $\mu g/m^3$	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
392 588 784	0.2 0.3 0.4	UV, UV	30-80 min (mouthpiece) CE (34.9, 61.8)	Progressive impairment of lung function with increasing effective dose; questionable significance during CE (61.8).	8 male	Adams et al., 1981
392 686	0.20 0.35	UV, UV	1 hr (mouthpiece) IE (77.5) @ variable competitive intervals CE (77.5)	FVC, $FEV_{1.0}$, and FEF_{25-75} decreased, subjective symptoms increased with O_3 concentration; f_B increased and V_T decreased during CE; no effect on $\dot{V}O_2$, HR, $\dot{V}_E$, or $\dot{V}_A$. No exposure mode effect.	10 male (distance runners)	Adams and Schelegle, 1983
392 823 980	0.2 0.42 0.50	UV, UV	2 hr IE (30 for male, 18 for female subjects) @ 15-min intervals	Pre-exposure to 0.2 ppm did not alter response to higher concentrations; $FEV_{1.0}$ decreased in sensitive subjects (n = 9) at 0.2 ppm; no significant sex differences.	8 male 13 female	Gliner et al., 1983
392 784	0.2 0.4	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	SR_{aw} increased with histamine challenge in 4 subjects at 0.4 ppm. "Adaptation" shown with repeated exposures.	12 male 7 female (divided into three exposure groups)	Dimeo et al., 1981
412	0.21	UV, UV	1 hr CE (81)	Decreases in FVC (6.9%), $FEV_{1.0}$ (14.8%), $FEF_{25-75\%}$ (18%), IC (11%), and MVV (17%). Symptoms reported: laryngeal and tracheal irritation, soreness, and chest tightness on inspiration.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
490 980 1470	0.25 0.50 0.75	CHEM, NBKI	2 hr R (8)	Spirometry: FVC, $FEV_{1.0}$, and MMFR decreased immediately following 0.75 ppm; FVC and $FEV_{1.0}$ decreased immediately following 0.5 ppm. Metabolism: respiratory exchange ratio and ventilatory equivalent increased (0.75 ppm); oxygen uptake decreased at all O_3 concentrations. Increased $\dot{V}_E$ during exposure facilitates decrement in lung function but does not facilitate return to normal following exposure. No effect on max $\dot{V}O_2$ following exposure.	8 male 7 female	Horvath et al., 1979

TABLE 11-2. STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978 (continued)

Ozone concentration $\mu g/m^3$	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
588 980	0.3 0.5	CHEM, NBKI	2 hr R	SG_{aw} decreased at 0.3 and 0.5 ppm. Tendency toward increased bronchial reactivity to ACh challenge. Smoking effects were similar to those of ozone.	6 male (equally divided by smoking history)	Kagawa and Tsuru, 1979a
588	0.3	MAST, BAKI	1 hr (mouthpiece) CE (34.7 for female and 51 for male subjects)	FVC, $FEV_{1.0}$ and $FEF_{25-75\%}$ decreased; f_B increased and V_T decreased with exercise; nonsmokers and females may be more sensitive; increase in subjective complaints noted.	12 male 12 female (equally divided by smoking history)	DeLucia et al., 1983
784	0.4	CHEM, NBKI	3 hr IE (4-5xR) for 15 min	FVC and $FEV_{1.0}$ decreased and bronchial reactivity to methacholine increased following exposure. Adaptation shown with repeated exposure.	13 male 11 female (divided into 2 phases)	Kulle et al., 1982b Kulle, 1983
1176	0.6	UV, NBKI	2 hr (noseclip) IE (2xR) @ 15-min intervals	SR_{aw} increased in nonatopic subjects ($n = 7$) with histamine and methacholine and in atopic subjects ($n = 9$) with histamine following exposure, returning to control values by the following day; response prevented by pretreatment with atropine aerosol.	11 male 5 female (divided by history of atopy)	Holtzman et al., 1979

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[a] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; BAKI = boric acid potassium iodide; UV = ultraviolet photometry.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] See Glossary for the definition of symbols.

Specific airway conductance was measured and samples of arterialized ear lobe capillary blood were taken for determinations of oxygen tension (PO_2) before and after the exposures. No changes in PO_2 or SG_{aw} were observed. Subjective symptoms (substernal burning) were reported by two individuals at 196 $\mu g/m^3$ (0.1 ppm), by three at 627 $\mu g/m^3$ (0.32 ppm), and by eight at 1960 $\mu g/m^3$ (1.0 ppm) of O_3.

11.2.2 Exposures With Exercise

The majority of controlled human studies since 1978 have been concerned with the effects of combined rest and exercise exposures to various concentrations of O_3 for variable periods of time (Table 11-2). Exercise during these exposures has been at different intensities and at different times during the exposures. The level of minute ventilation ($\dot{V}_E$), which varies with exercise intensity, is a primary determinant of the magnitude of pulmonary effects resulting from exposure to a given level of O_3. Therefore, results from studies using different regimens of exercise, even with exposure to the same O_3 concentration, may be difficult to compare. Most studies used alternating 15-min periods of rest and exercise. Pulmonary function and/or subjective symptoms were usually measured pre- and post-exposure. In a few studies, such measurements were also made during the rest periods after each exercise period. Exposures in these studies were usually performed only on one day, and were therefore likely to induce smaller functional decrements than would have been observed if subjects had been exposed on two sequential days, as noted in Section 11.3 entitled "Pulmonary Effects Following Repeated Exposures."

Other factors that may influence the results obtained by different investigators and account for some of the inconsistencies observed among the findings from various studies are discussed in this chapter. Such factors include experimental design (more specifically: number of subjects, exposure time, recurrent exposures, length of and sequencing of exercise periods, and time of measurements), and specific measurement techniques used to determine O_3 concentration (see Chapter 5) and to characterize pulmonary responses. The variability of intrinsic responsiveness of individual subjects to O_3, effects of O_3 on subjects with pulmonary disease, and other factors affecting the responsiveness of subjects to O_3, such as smoking history, sex, and environmental conditions, are discussed in this section. Studies on the interaction between O_3 and other pollutants are presented in Section 11.5.

As previously stated, increased $\dot{V}_E$ accompanying exercise is one of the most important contributors to pulmonary decrements during O_3 exposure. While the more recent reports include actual measurements of $\dot{V}_E$ obtained during exposure, earlier publications often included only a description of the exercise regimen. Table 11-3 may aid the reader in estimating the $\dot{V}_E$ associated with a given exercise regimen.

The values for O_2 consumption and $\dot{V}_E$ in Table 11-3 are approximate estimates for average physically fit males exercising on a bicycle ergometer at 50 to 60 rpm (if rpms are higher or lower, values may be different). Note that individual variability is great and that the level of physical fitness, age, level of training, and other physiological factors may modify the estimated values. The only precise method of obtaining these data is to actually measure the $\dot{V}_E$ and O_2 consumption. If exercise is conducted on a treadmill, adequate relative standards for O_2 consumption and $\dot{V}_E$ can not be estimated. Thus, with such activity, there is an absolute need to measure these variables.

Bates et al. (1972) and Bates and Hazucha (1973), as described in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978), were the first to consider the role of increased ventilation due to exercising in an O_3 environment. These observations emphasized an important aspect of ambient exposure; namely, that individuals who are engaged in some type of activity during ambient exposure to polluted air experience greater pulmonary function decrement than resting individuals.

Hazucha et al. (1973) reported data obtained on 12 subjects exposed for 2 hr to either 725 (n=6) or 1470 (n=6) $\mu g/m^3$ (0.37 or 0.75 ppm) of O_3. These subjects performed light exercise ($\dot{V}_E$ reported to be double resting ventilation) alternately every 15 minutes. Three subjects also had total lung capacity (TLC), residual volume (RV), and closing capacity (CC) measured before and after 2-hr exposure to 1470 $\mu g/m^3$ (0.75 ppm) of O_3. Significant decreases in lung function derived from the measurements of forced expiratory spirometry were observed at both 0.37 ppm ($P < 0.05$) and 0.75 ppm ($P < 0.001$) of O_3; the decrease was greater at the higher level of O_3. After exposures, all subjects complained to varying degrees of substernal soreness, chest tightness, and cough. While the number of subjects was small and the results therefore inconclusive, RV and CC increased and TLC was unchanged after exposure to 0.75 ppm of O_3.

TABLE 11-3. ESTIMATED VALUES OF OXYGEN CONSUMPTION AND MINUTE VENTILATION ASSOCIATED WITH LEVELS OF EXERCISE[a]

Level of work	Watts	Kgm/min[b]	O_2 consumption (L/min)	Minute ventilation (L/min)	Representative activities[c]
Light	25	150	0.65	13	Level walking at 2 mph; washing clothes
Light	50	300	0.96	19	Level walking at 3 mph; bowling; scrubbing floors
Light	75	450	1.25	25	Dancing; pushing wheelbarrow with 15-kg load; simple construction; stacking firewood
Moderate	100	600	1.54	30	Easy cycling; pushing wheelbarrow with 75-kg load; using sledgehammer
Moderate	125	750	1.83	35	Climbing stairs; playing tennis; digging with spade
Moderate	150	900	2.12	40	Cycling at 13 mph; walking on snow; digging trenches
Heavy	175	1050	2.47	55	Cross-country skiing; rock climbing; stair climbing with load; playing squash and handball; chopping with axe
Heavy	200	1200	2.83	63	
Very heavy	225	1350	3.19	72	
Very heavy	250	1500	3.55	85	Level running at 10 mph; competitive cycling
Severe	300	1800	4.27	100+	Competitive long distance running; cross-country skiing

[a] See text for discussion.

[b] Kgm/min = work performed each minute to move a mass of 1 kg through a vertical distance of 1 m against the force of gravity.

[c] Adapted from Åstrand and Rodahl (1977).

Kerr et al. (1975) reported small, but significant, decreases in FVC, $FEV_{3.0}$, R_L, and SG_{aw} when 20 subjects were exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for 6 hr with two 15-min periods of medium exercise (100 W). The symptoms of dry cough and chest discomfort were also experienced after exposure. No changes in TLC, RV, C_{st}, dN_2, or D_LCO were observed.

Von Nieding et al. (1977) exposed normal subjects to 196 $\mu g/m^3$ (0.1 ppm) O_3 for 2 hr with light intermittent exercise and found no changes in either forced expiratory functions or symptoms. However, they found significant increases (~ 7 mm Hg) in both alveolar-arterial PO_2 difference and airway resistance (~ 0.5 cm $H_2O/L/s$).

Folinsbee et al. (1977b) demonstrated that the heightened pulmonary effect of O_3 associated with intermittent exercise during exposure occurred principally, if not entirely, during the exercise period. In this study, involving subjects who had exercised for a single 30-min period during a 2-hr 980-$\mu g/m^3$ (0.50-ppm) O_3 exposure, the maximum impairment of forced expiratory spirometry appeared immediately (2 to 4 min) after exercise (Figure 11-1). Despite continued exposure to O_3, but at rest, pulmonary function either improved or showed no further impairment. No change in RV or R_{aw} was observed, while TLC was reduced.

Folinsbee et al. (1978) reported results from 40 subjects in studies designed to evaluate the effects of various concentrations of O_3 at several different levels of activity from rest through heavy exercise. Half of the subjects had previously resided in an area having high O_3 concentrations; 14 reported symptoms associated with irritation or breathing difficulty on high-pollution days. Five subjects who had not resided in such areas reported similar symptoms upon visiting a high-oxidant-pollution region. Nine subjects had a history of allergy, 11 were former smokers, and one had had asthma as a child. Ten subjects in each of four groups were exposed four times, in random order, to filtered air or 196, 588, or 980 $\mu g/m^3$ (0, 0.10, 0.30, or 0.50 ppm) of O_3. One group rested throughout the exposure. The other three groups exercised at four intervals throughout the exposure; each 15-min exercise period was followed by a 15-min rest period. Each subject in the three exercise groups walked on a treadmill at a level of activity to produce minute ventilations of approximately 30, 50, or 70 L/min, respectively. The integrated minute ventilatory volumes for the total 2 hr of exposure were 10, 20.35, 29.8, and 38.65 L, respectively. No pulmonary changes were observed with

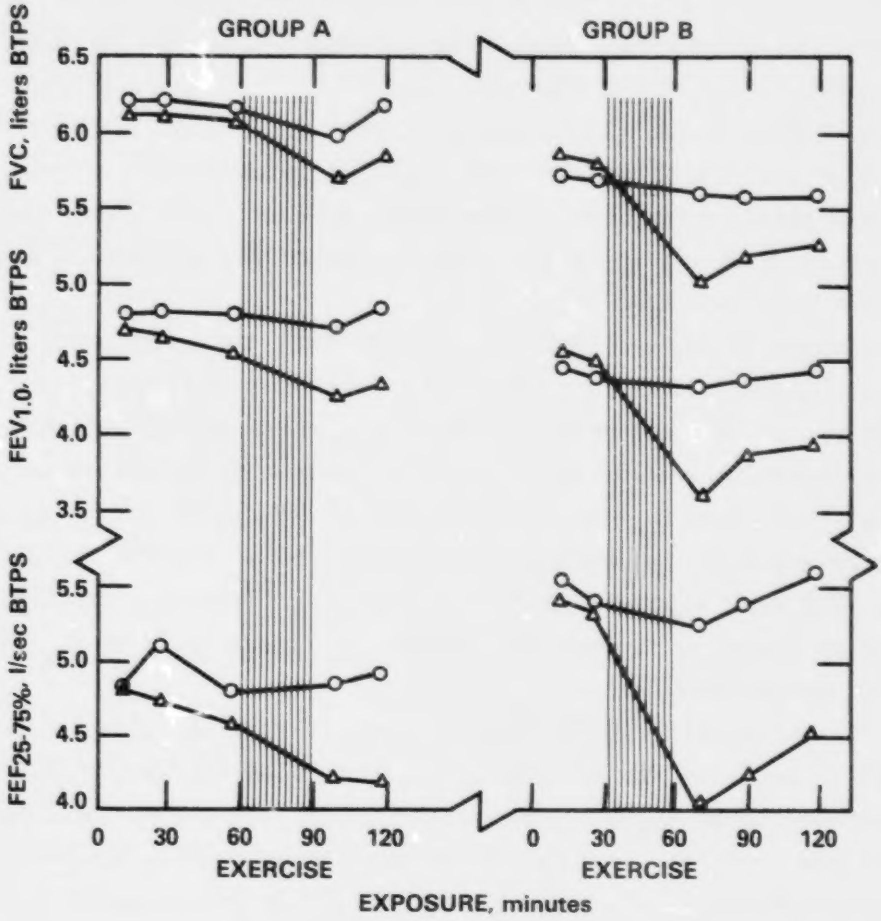

Figure 11-1. Change in forced vital capacity (FVC), forced expiratory volume in 1-sec (FEV $_{1.0}$), and maximal mid-expiratory flow (FEF$_{25-75\%}$) during exposure to filtered air (○) or ozone (△) (0.5 ppm) for 2 hr. Exercise at 45% maximal aerobic capacity (max VO_2) was performed for 30 min by Group A after 60 min of ozone exposure and by Group B after 30 min of ozone exposure.
Source: Folinsbee et al. (1977b).

exposure to filtered air or 196 μg/m^3 (0.10 ppm) of O_3. At rest (10 L/min), pulmonary function changes were confined to 980 μg/m^3 (0.50 ppm) O_3 exposures. Some changes were apparent at the lowest work load (30 L/min) and 588 μg/m^3 (0.30 ppm) of O_3, and effects were more marked at 980 μg/m^3 (0.50 ppm) of O_3. At the two highest work loads (49 and 67 L/min), pulmonary function changes occurred at both 588 and 980 μg/m^3 (0.30 and 0.50 ppm), with the changes at 980 μg/m^3 (0.50 ppm) of O_3 usually significantly greater than those at 588 μg/m^3 (0.30 ppm) of O_3. During exercise, respiratory frequency was greater and tidal volume lower with O_3 exposure than with sham exposure. The change in respiratory pattern was progressive and was most striking at the two heaviest work loads and at the highest O_3 concentrations. Reductions in TLC and inspiratory capacity (IC), but not RV or functional residual capacity (FRC), were also noted.

In a study similar to that of von Nieding et al. (1977), Linn et al. (1979) exposed normal subjects to 392 μg/m^3 (0.2 ppm) of O_3. The 12 subjects had blood and alveolar gas samples taken shortly after 1 and 2 hr of their 2.5 hr of exposure. These subjects also exercised at twice resting ventilation for 15 min of every half hour. Blood samples were taken both from an arterialized ear lobe and a brachial artery. Alveolar PO_2 exhibited no changes with time or exposure. Brachial artery PO_2 showed highly significant variations with time, decreasing between the 0 and 1-hr samples and being partially reversed at 2 hr. The alveolar-arterial oxygen pressure difference [$P(A-a)O_2$] was increased at 1 hr and reversed at 2 hr. This pattern was seen on both the no-O_3 and O_3 exposure days. Ear lobe sample data showed some differences but were not related to O_3 exposure. In six subjects (bringing the total number of subjects exposed to 18) on whom both ear lobe and arterial samples were obtained, the authors reported a significant change in arterial PO_2. An explanation for the differences in response of the $P(A-a)O_2$ obtained by these two groups of investigators was not readily apparent.

Adams et al. (1981) required eight subjects (22 to 46 years of age) to exercise continuously (i.e., no rest periods) while orally inhaling 0.0, 392, 588, and 784 μg/m^3 (0.0, 0.2, 0.3, and 0.4 ppm) of O_3. The duration of the exercise periods varied from 30 to 80 min, and the two exercise loads were sufficient to induce minute ventilations of 34.9 and 61.8 L/min, respectively. Pulmonary functions were measured before and within 15 min after exercise At both minute ventilations, decrements in forced expiratory spirometry were observed for exposures to 588 and 784 μg/m^3 (0.30 and 0.40 ppm) of O_3 with the magnitude of decrement greater at the higher minute ventilation. The magnitude of decrement also increased with increasing exposure time. No pulmonary effects were observed for exposures to clean air or 392 μg/m^3 (0.2 ppm) of O_3. The authors suggested that the detectable level for O_3 functional effects in healthy subjects during sustained exercise at a moderately heavy work load ($\dot{V}_E$ of ~62 L/min) occurred between O_3 concentrations of 392 and 588 μg/m^3 (0.2 and 0.3 ppm). The responses to continuous exercise were similar to those observed in studies using intermittent but equivalent exercise.

Kagawa (1983a) presented data on 15 subjects exercising intermittently (15 min exercise, 15 min rest) during a 2-hr exposure to 294 or 588 μg/m^3 (0.15 or 0.30 ppm) of O_3. These subjects reported the typical symptoms at the higher O_3 concentrations. Paired t-tests were used to compare responses to filtered air and O_3. SG_{aw} decreased 6.4 percent ($P < 0.05$) following the 294-μg/m^3 (0.15-ppm) exposure and 16.7 percent ($P < 0.01$) following the 588-μg/m^3 (0.30-ppm) exposure. In the latter environment, only FVC showed a significant ($P < 0.05$) decrement; FEV_1 was unaffected. These subjects had resided in a low-oxidant-pollutant environment.

McDonnell et al. (1983) provided further information related to high levels of ventilation during exercise in 135 subjects exposed to O_3. They divided their subjects into six groups, each group exposed to a different concentration of O_3; viz. 0.0 (n=20), 0.12 (n=22), 0.18 (n=20), 0.24 (n=21), 0.30 (n=21), and 0.40 (n=29) ppm, equivalent to 0.0, 235, 353, 470, 588, and 784 μg/m^3 of O_3. The subjects were exposed for 2.5 hr, with exposure consisting of alternating 15-min periods of rest and exercise ($\dot{V}_E$/BSA of ≅ 35 L/m^2 or $\dot{V}_E$ = 64 to 68 L/min) during the first 2 hr. With continued O_3 exposure, forced expiratory spirometry and pulmonary symptoms were measured between 5 and 10 min after the final exercise, while plethysmography was performed between 25 and 30 min after the final exercise. The pulmonary symptom, cough, showed the greatest sensitivity to O_3 (it occurred at the lowest concentration, 235 μg/m^3 or 0.12 ppm of O_3). Small changes in forced expiratory spirometric measures (FVC, FEV_1, maximal mid-expiratory flow [$FEF_{25-75\%}$]) were suggested at 235 μg/m^3 (0.12 ppm) of O_3 and were definitely present at 353 μg/m^3 (0.18 ppm) of O_3. Greater changes were found at and above 470 μg/m^3 (0.24 ppm) of O_3. Significant decreases in tidal volume (V_T) and increases in respiratory frequency (f_R) during exercise (similar changes had been reported by other investigators) and specific airway resistance (SR_{aw}), pain on deep inspiration, and shortness of breath occurred at O_3 levels of >470 μg/m^3 (0.24 ppm). The sigmoid-shaped dose-response curves indicated a relatively large decrease in FVC, FEV_1, and $FEF_{25-75\%}$ between 353 and 470 μg/m^3 (0.18 and 0.24 ppm) O_3. However, in contrast to the results of other investigations, a plateau in response was observed at the higher levels (>470 μg/m^3; 0.24 ppm) of O_3. In contrast to the spirometric tests, SR_{aw} increased significantly at 470 μg/m^3 (0.24 ppm) of O_3 and continually increased with increasing O_3 levels, in agreement with the results of other investigators. These two different patterns in response plus the observation that individual changes in SR_{aw} and FVC were poorly correlated prompted these investigators to suggest that more than a single mechanism might have to be implicated to define the effects of O_3 on pulmonary functions. Findings from this study are particularly relevant in that a large subject population was studied and pulmonary effects were present at an O_3 concentration (235 μg/m^3; 0.12 ppm) lower than that for which they had previously been observed.

More recent studies on well-trained subjects have become available. Six well-trained men and one well-trained woman (all of the subjects except one male being a competitive distance cyclist) exercised continuously on a bicycle ergometer for 1 hr while breathing filtered air or 412 μg/m^3 (0.21 ppm) of O_3 (Folinsbee et al., 1984). They worked at 75 percent maximal aerobic capacity (max $\dot{V}_{O2}$) with mean minute ventilations of 89 L/min. Pulmonary function measurements were made pre- and post-exposure. Decreases occurred in FVC (6.9 percent), $FEV_{1.0}$ (14.8 percent), $FEF_{25-75\%}$ (18 percent), IC (11 percent), and maximum voluntary ventilation (MVV) (17 percent). The magnitude of these changes were of the same order as those observed in subjects performing moderate intermittent exercise for 2 hr in a 686-μg/m^3 (0.35-ppm) O_3 environment. Symptoms included laryngeal and/or tracheal irritation and soreness as well as chest tightness upon taking a deep breath.

Adams and Schelegle (1983) exposed 10 well-trained distance runners to 0.0, 392, and 686 μg/m^3 (0.0, 0.20, and 0.35 ppm) of O_3 while the runners exercised on a bicycle ergometer at work loads simulating either a 1-hr steady-state training bout or a 30-min warmup followed immediately by a 30-min competitive bout. These exercise levels were of sufficient magnitude (68 percent of their max $\dot{V}_{O2}$) to increase mean $\dot{V}_E$ to 80 L/min. In the last 30 min of the competitive exercise bout, minute ventilations were approximately 105 L/min. Subjective symptoms, including shortness of breath, cough, and raspy throat increased as a function of O_3 concentration for both continuous and competitive levels. The high ventilation volumes (80 L/min) resulted in marked pulmonary function impairment and altered ventilatory patterns (increased f_R and decreased V_T) when exercise was performed in 392 $\mu g/m^3$ (0.20 ppm) of O_3. Two-way analysis of variance (ANOVA) procedures performed on the pulmonary function data indicated significant decrements ($P < 0.0002$) for FVC, FEV_1, and $FEF_{25-75\%}$. These investigators noted that percent decrement in $FEV_{1.0}$ was similar to that observed by Folinsbee et al. (1978) when the two studies were compared on the basis of effective dose. The concept of effective dose will be treated in a later section.

11.2.3 Intersubject Variability and Reproducibility of Responses

In the majority of the above studies, assessment of the significance of results was typically based on the mean ± variance of changes in lung function resulting from exposure to O_3 as compared to exposure to clean air. Although consideration of mean changes is useful for making statistical inferences about homogeneous populations, it may not be adequate to describe the differences in responsiveness to O_3 among individuals. While the significant mean changes observed demonstrate that the differences in response between O_3 and clean air exposures were not due to chance, the variance of responses was quite large in most studies. Characterization of reports of individual responses to O_3 is pertinent since it permits the assessment of the proportion of the population that may actually be affected during exposure to O_3.

Results from a small number of studies (Horvath et al., 1981; Gliner et al., 1983; McDonnell et al., 1983) that have reported individual responses indicate that a considerable amount of intersubject variability does exist in the magnitude of response to O_3. Figure 11-2 illustrates the variability of responses in $FEV_{1.0}$ and SR_{aw} obtained from subjects exposed to different O_3 concentrations.

Decreases in $FEV_{1.0}$ ranging from 2 to 48 percent (mean = 18 percent) were reported by Horvath et al. (1981) for 24 subjects exposed for 2 hours to 823 $\mu g/m^3$ (0.42 ppm) of O_3 while performing moderate intermittent exercise. When these same subjects were exposed to clean air under the same conditions, the response of $FEV_{1.0}$ ranged from an 8-percent increase to an 11-percent decrease (mean = 0 percent).

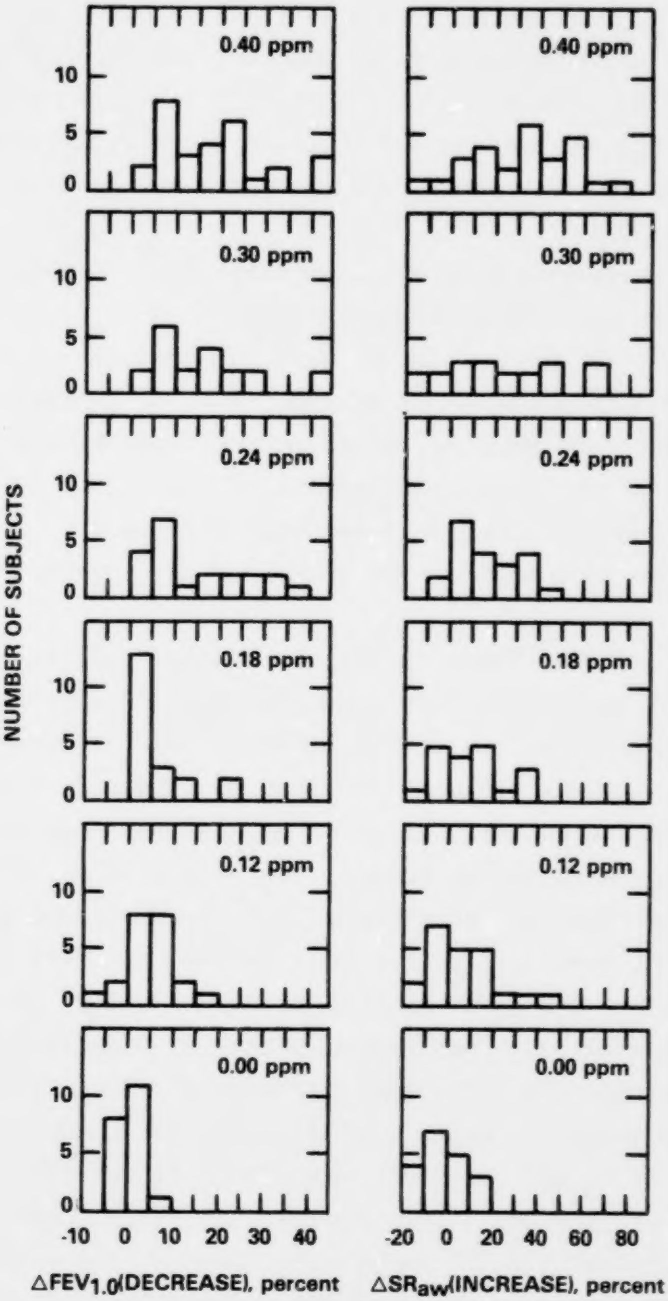

Figure 11-2. Frequency distributions of response (percent change from baseline) in specific airway resistance (SR_{aw}) and forced expiratory volume in 1-sec ($FEV_{1.0}$) for individuals exposed to six levels of ozone. One individual with 260% increase in SR_{aw} exposed to 0.4 ppm of ozone is not graphed.
Source: McDonnell et al. (1983).

Gliner et al. (1983) exposed subjects (13 females, 8 males) performing intermittent light exercise for 2 hr to clean air and 392 $\mu g/m^3$ (0.20 ppm) of O_3. Changes in $FEV_{1.0}$ resulting from clean-air exposure ranged between +7.8 percent and -7.5 percent (mean = 0 percent), while the range of changes in $FEV_{1.0}$ was +6.0 to -16.6 percent (mean = -4 percent) with exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3.

For subjects performing 2 hr of intermittent heavy exercise while exposed to O_3, McDonnell et al. (1983) observed changes in $FEV_{1.0}$ ranging from -3 to -43 percent (mean = -16 percent) at 784 $\mu g/m^3$ (0.40 ppm), -4 to -38 percent (mean = -17 percent) at 588 $\mu g/m^3$ (0.30 ppm), -2 to -41 percent (mean = -15 percent) at 470 $\mu g/m^3$ (0.24 ppm), -2 to -22 percent (mean = -7 percent) at 353 $\mu g/m^3$ (0.18 ppm), +7 to -17 percent (mean = -4 percent) at 235 $\mu g/m^3$ (0.12 ppm), and +3 to -7 percent (mean = -2 percent) in clean air. Large intersubject variability was also reported for changes in SR_{aw} during these exposures (Figure 11-2).

The factors that contribute to the observed variability of individual responses have not been identified. One factor to be considered is real intersubject differences in the stable intrinsic level of responsiveness to O_3. The degree to which a subject's response to a given O_3 concentration can be reproduced is an indication of how precisely the measured response estimates that subject's intrinsic responsiveness. In a 1983 study, Gliner et al. exposed subjects performing intermittent light exercise for 2 hr to 392 $\mu g/m^3$ (0.20 ppm) of O_3 on three consecutive days, followed the next day by an exposure to either 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3. Each subject had also been exposed prior to or was exposed after the study to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) O_3. For individual responses of $FEV_{1.0}$, a moderate correlation (r = 0.58) between changes resulting from the first exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3 and the first exposure to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3 was observed. When responses in $FEV_{1.0}$ from the first and second exposures to 0.42 or 0.50 ppm O_3 were compared, the correlation between the two exposures was quite high (r = 0.92). Although these comparisons were confounded by possible effects of prior O_3 exposure, they do suggest that individual changes in $FEV_{1.0}$ resulting from O_3 exposure are reasonably reproducible. Moreover, a given individual's response to a single O_3 exposure is probably a reliable estimate of that individual's intrinsic responsiveness to O_3.

11.2.4 Prediction of Acute Pulmonary Effects

Nomograms for predicting changes in lung function resulting from the performance of light intermittent exercise while exposed to different O_3 concentrations were included in one of the earliest reports of the effects of O_3 on normal subjects (Bates and Hazucha, 1973). Then in 1976, Silverman et al. reported that pulmonary function decrements were related as linear and second-order polynomial functions of the effective dose of O_3, defined as the product of concentration, exposure duration, and $\dot{V}_E$. Equations were derived from lung function measurements at 1 and 2 hr of exposure to 725, 980, and 1470 $\mu g/m^3$ (0.37, 0.50, and 0.75 ppm) of O_3 under conditions of both rest and intermittent exercise sufficient to increase $\dot{V}_E$ by a factor of 2.5. Although the fit of their data to linear and second-order curves was good, the authors also commented that for a given effective dose, exposure to a high concentration of O_3 for a short period of time induced greater functional decrements than a longer exposure to a lower concentration. This phenomenon implies that O_3 concentration is a more important contributor to response than is exposure duration. Moreover, they also observed extensive individual variability in pulmonary function changes, suggesting that use of effective dose is not satisfactory for predicting individual responses to O_3 exposure.

Since the inception of the concept of an effective dose, additional studies have used, and in some cases refined, it for prediction of pulmonary responses to O_3 exposure. Extension of the effective-dose concept was accomplished in the studies of Folinsbee et al. (1978) on subjects at rest and performing intermittent exercise during 2-hr exposures to 0, 196, 588, and 980 $\mu g/m^3$ (0.0, 0.10, 0.30, and 0.50 ppm) of O_3. The exercise loads required $\dot{V}_E$ of some three, five, and seven times greater than resting ventilations. Again, the effective dose was calculated as the product of O_3 concentration x $\dot{V}_E$ (L/min) during exposure (includes both exercise and rest minute ventilation) x duration of exposure. Polynomial regression analyses were performed first on mean data at each level of $\dot{V}_E$, and second on all subject groups together after computing the effective dose. Figure 11-3 (an example of the calculations made) presents the linear and polynomial regression lines for percent change in pulmonary functions (FVC and $FEV_{1.0}$) as a function of O_3 concentration during the 2-hr exposure. Figure 11-4 presents the polynomial regression lines for percentage change in $FEV_{1.0}$ as a function of "effective dose" of O_3. Data from other investigators are also presented. Predictions of pulmonary function changes in FEV_1 based on effective doses up to 1.5 ml O_3 agreed with

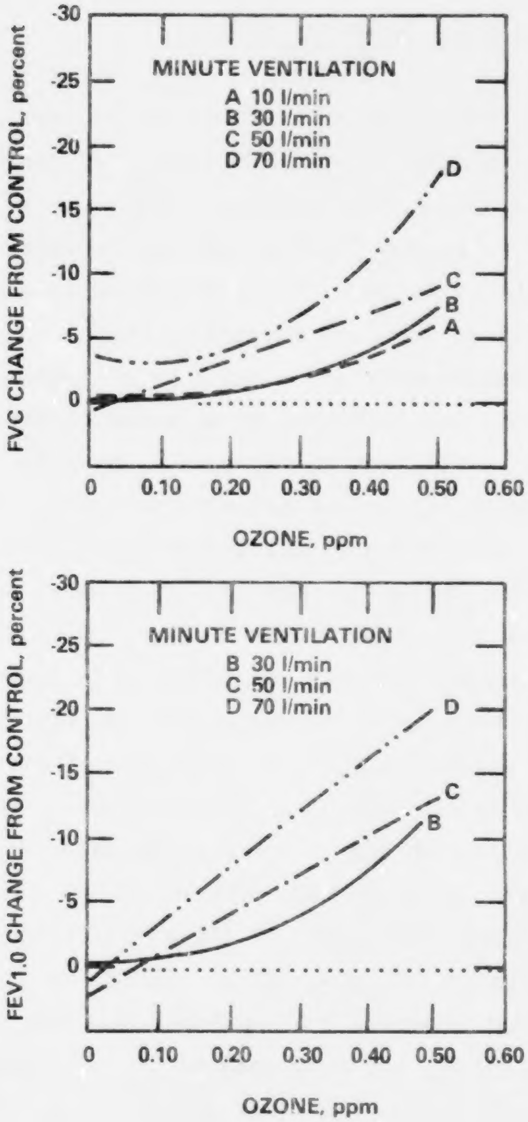

Figure 11-3. Linear and polynomial regression lines for percentage change in pulmonary function [forced vital capacity (FVC) and 1-sec forced expiratory volume $(FEV_{1.0})$] as a function of ozone concentration during a 2-hr exposure with intermittent exercise. Letters indicate groups in which exercise levels were adjusted to achieve a given minute ventilation: A (rest), B (30 l/min), C (50 l/min), and D (70 l/min). Nonsignificant lines were omitted.
Source: Folinsbee et al. (1978).

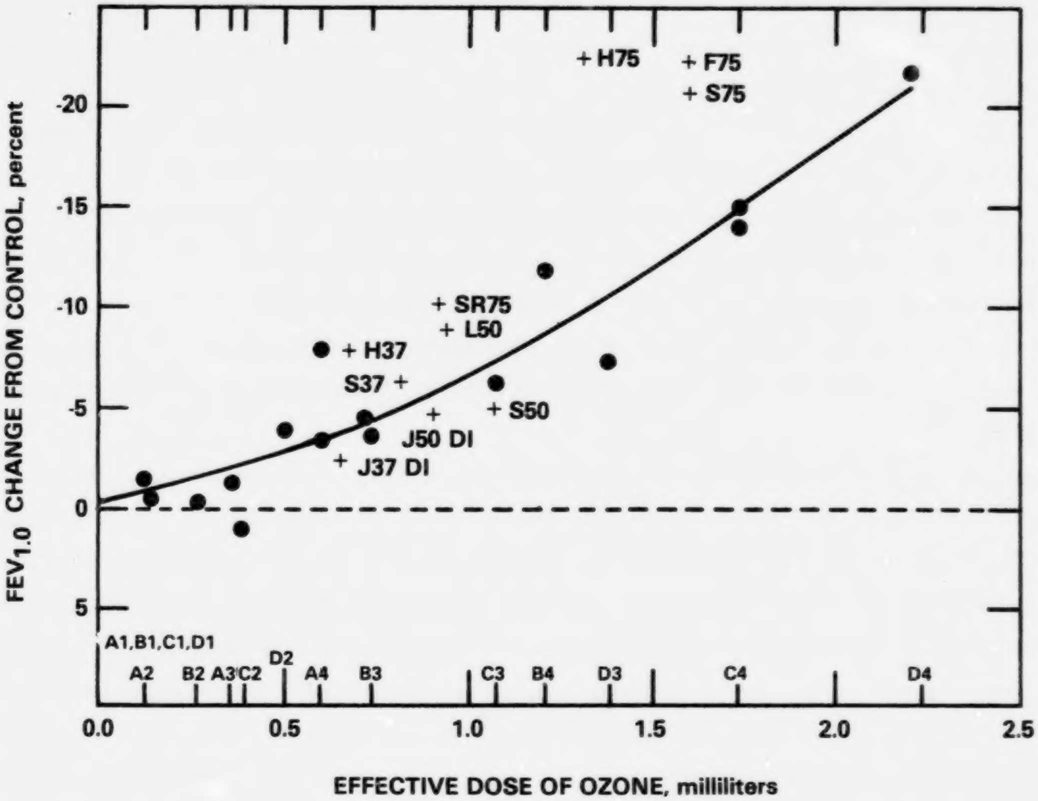

Figure 11-4. Polynomial regression line of percentage change in 1-sec forced expiratory volume ($FEV_{1.0}$) as a function of "effective dose" of ozone calculated as the product of ozone concentration (ppm), minute ventilation (l/min), and exposure time (min). A, B, C, D, and subgroups (●) = Folinsbee et al., 1978; other studies (+) are H = Hazucha et al., 1973; S = Silverman et al., 1976; F = Folinsbee et al., 1977a; J = Hackney et al., 1975c; L = Folinsbee et al., 1977b; for which accompanying numbers indicate ozone concentrations in pphm. DI after J37 and J50 refers to the first of two exposure days. SR75 refers to resting exposure at 0.75 ppm from reference S.

Source: Adapted from Folinsbee et al. (1978).

data collected by other investigators. Prediction equations using the effective dose for all measured pulmonary functions were constructed. All equations were significant at the 0.01 level. These investigators also used a multiple regression approach to refine further the prediction of changes in pulmonary function resulting from O_3 exposure. Duration of exposure was not analyzed as a contributing factor since all exposures were of equal time. Their analyses indicate that essentially all of the variance of pulmonary responses could be explained by O_3 concentration and $\dot{V}_E$. For example, these two predictors accounted for approximately 80 percent (multiple r = 0.89) of the variance in $FEV_{1.0}$. Moreover, O_3 concentration accounted for more of variance than did $\dot{V}_E$, and for a given effective dose, exposure to a high concentration with a low $\dot{V}_E$ induced greater functional decrements than exposure to a lower concentration with elevated $\dot{V}_E$. Equations (with appropriately weighted O_3 concentration and $\dot{V}_E$) for predicting the magnitude of pulmonary decrements were also provided.

Adams et al. (1981) further extended the effective-dose concept in studies using a multiple regression approach and arrived at essentially the same conclusions reached by Folinsbee et al. (1978), namely that most of the variance for pulmonary function variables could be accounted for by O_3 concentration, followed by $\dot{V}_E$, and then by exposure time. Adams et al. emphasized the predominant importance of O_3 concentration and suggested that the detectable level for O_3 functional effects in healthy subjects during sustained exercise at a moderately heavy work load ($\dot{V}_E \sim 62$ L) occurred between O_3 concentrations of 392 and 588 $\mu g/m^3$ (0.2 and 0.3 ppm). The responses to continuous exercise were similar to those observed in studies using intermittent but equivalent exercise. They also noted, as had others, that the effective-dose concept was not satisfactory for predicting individual responses.

Colucci (1983) assembled data available from the literature and analyzed them with the purpose of constructing dose/effects profiles for predicting pulmonary responses to O_3 based on results combined from many different laboratories. Basically, he examined changes in R_{aw} and $FEV_{1.0}$ as functions of exposure rate (O_3 concentration x $\dot{V}_E$) and total exposure dose (exposure rate x duration of exposure), which is equivalent to effective dose. The correlation for changes in R_{aw} was slightly better than that for changes in $FEV_{1.0}$. The author states that he elected to use linear equations to fit the data rather than polynomials because he found little difference in the degree of correlation between the two methods. This statement somewhat contradicts his observation of an attenuation in the rate of increase of SR_{aw} as $\dot{V}_E$ increased to higher levels; there was no attenuation of the decrease in $FEV_{1.0}$ as a function of increasing $\dot{V}_E$. This observation suggested to Colucci that different mechanisms may be involved in the effects on R_{aw} and $FEV_{1.0}$. Whether expressed as functions of exposure rate or total exposure dose, the patterns of pulmonary responses were approximately equivalent. This is not surprising since both Folinsbee et al. (1978) and Adams et al. (1981) had previously shown that most of the variance in pulmonary response depended primarily on O_3 concentration and $\dot{V}_E$. The overall finding, that increases in R_{aw} and decreases in $FEV_{1.0}$ are reasonably correlated with increases in effective dose of O_3, only confirms the results reported by previous investigators. As proposed by Folinsbee et al. (1978) and Adams et al. (1981), a better fit of the data may have been obtained had Colucci used multiple regression and equations that appropriately weighted the relative contributions of each of the exposure variables to pulmonary decrements.

11.2.5 Bronchial Reactivity

In addition to overt changes in pulmonary function, several studies have reported increased nonspecific airway sensitivity resulting from O_3 exposure. Airway responsiveness to the drugs acetylcholine (ACh), methacholine, or histamine is most often used to define nonspecific airway sensitivity.

Eight healthy nonsmoking men served as subjects (Golden et al., 1978) for evaluation of bronchial reactivity due to histamine after a 2-hr exposure to 1176 $\mu g/m^3$ (0.6 ppm) of O_3. The resting subjects breathed orally (a nose-clip was worn). These investigators concluded that O_3 exposure at this concentration and dose produced an enhanced response to histamine, which returned to normal within 1 to 3 weeks after exposure.

Kagawa and Tsuru (1979a) studied both smokers and nonsmokers exposed to 0.0, 588, and 980 $\mu g/m^3$ (0.0, 0.3, and 0.5 ppm) O_3. Their three nonsmoking subjects were exposed for 2 hr followed by measurements of bronchial reactivity to ACh. They found that these subjects demonstrated an increased reactivity to ACh. However, because of the small number of subjects and the large variability of responses, the results may not represent a significant effect.

The bronchial reactivity of atopic and nonatopic subjects was evaluated by Holtzman et al. (1979). They studied 16 healthy nonsmoking subjects and found that nine could be classified as "atopic" based on medical history and allergen skin testing. All subjects had normal pulmonary functions determined in preliminary screening tests and were asymptomatic. Both atopic and nonatopic subjects performed intermittent exercise while wearing noseclips and exposed by mouthpiece to filtered air and 1176 $\mu g/m^3$ (0.6 ppm) of O_3. Bronchial reactivity was determined 1 hr after exposure to each condition (when post-exposure SR_{aw} had returned to normal) by measuring the increase in SR_{aw} produced by inhalation of histamine or methacholine aerosols. In both atopic and nonatopic subjects, the bronchial response to histamine and methacholine was enhanced after O_3 exposure when compared to exposure in filtered air. The increase in SR_{aw} resulted predominantly from an increase in airway resistance, with only small changes in trapped gas volume. Symptoms of bronchial irritation were increased; however, these changes were transient, and were not detectable by the next day. This result contrasts with previous results observed by these investigators (Golden et al., 1978), which indicated that enhanced bronchial responsiveness persisted for a more prolonged period. Premedication with atropine sulfate aerosol prevented the increase in SR_{aw} histamine inhalation. Atopic subjects appeared to respond to a greater degree than nonatopic subjects, although the pattern of change and the induction and time course of increased bronchial reactivity after exposure to O_3 were unrelated to the presence of atopy.

König et al. (1980) exposed 14 healthy nonsmokers (13 men, 1 woman) for 2 hr to 0, 196, 627, and 1960 $\mu g/m^3$ (0.0, 0.10, 0.32, and 1.00 ppm) of O_3. Bronchial reactivity to ACh was determined after exposure. Significant increases in bronchial reactivity were observed with the ACh challenge at 627 $\mu g/m^3$ (0.32 ppm) and 1960 $\mu g/m^3$ (1.0 ppm) of O_3.

Bronchial reactivity of normal adult subjects was assessed by measuring the increase in SR_{aw} produced by inhalation of histamine aerosol (Dimeo et al., 1981). Seven subjects, intermittently exercising (15 min exercise, 15 min rest) at a load sufficient to double their resting $\dot{V}_E$, were exposed to 392 $\mu g/m^3$ (0.2 ppm) of O_3 over a 2-hr period. Two air exposures preceded the O_3 exposure, which was followed by another air exposure. Another group (five individuals) were only repeatedly tested pre- and post-air exposure for their response to histamine. In these two groups, the bronchial responsiveness to histamine was not different in the air exposures. The bronchomotor response to inhaled histamine aerosol was not altered following the 392-$\mu g/m^3$ (0.2-ppm) O_3 exposure. However, a third group (seven individuals) was also exposed to air for 2 days and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the following day. The mean bronchial responsiveness to inhaled histamine was increased following exposure to 784 $\mu g/m^3$ (0.4 ppm) of O_3. Baseline SR_{aw} (i.e., before histamine) after the 0.4-ppm exposure remained unchanged.

As part of a study of repeated exposures to O_3 (discussed in detail in Section 11.3), Kulle et al. (1982b) exposed two separate groups of subjects (13 males, 11 females) for 3 hr to filtered air and then 1 week later to 784 $\mu g/m^3$ (0.4 ppm) of O_3. One hour before the end of exposure, 15 min of exercise at 100 W was performed approximating a $\dot{V}_E$ of four to five times resting values. Bronchial reactivity to methacholine was assessed after each exposure and was significantly enhanced ($P < 0.01$) in both subject groups following exposure to O_3 as compared to filtered-air exposure.

11.2.6 Mechanisms of Acute Pulmonary Effects

The primary acute respiratory responses to O_3 exposure are decrements in variables derived from measures of forced expiratory spirometry (volumes and flows) and respiratory symptoms (notably, cough and substernal pain upon deep inspiration). Altered ventilatory control during exercise (increased f_R and decreased V_T with $\dot{V}_E$ remaining unchanged) and small increases in airway resistance have also been observed.

Decrements in FVC observed at relatively high (1470-$\mu g/m^3$; 0.75-ppm) O_3 concentrations have been associated with increases in RV (Hazucha et al., 1973; Silverman et al., 1976). Since increased RV occurs only at higher O_3 concentrations, it has been postulated by Hazucha et al. (1973) that this increase results from gas trapping and premature airway closure caused by a direct effect of O_3 on small airway smooth muscle or by interstitial pulmonary edema.

At O_3 concentrations of 980 $\mu g/m^3$ (0.50 ppm) and less, decrements in FVC are related to decreases in TLC without changes in RV. Decreased TLC results from reductions in maximal expiratory position as indicated by the observation that inspiratory capacity also declines (Hackney et al., 1975c; Folinsbee et al., 1977b; Folinsbee et al., 1978). Moreover, a decrease in inspiratory effort, rather than a decrease in lung compliance, most likely causes the reduced inspiratory capacity resulting from O_3 exposure (Bates and Hazucha, 1973; Silverman et al., 1976; Folinsbee et al., 1978). Ozone is thought to "sensitize" or stimulate irritant (rapidly adapting) and possibly other airway receptors (Folinsbee et al., 1978; Golden et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). This results in vagally mediated inhibition of maximal inspiration, either involuntarily or due to discomfort (Bates et al., 1972; Silverman et al., 1976; Folinsbee et al., 1978; Adams et al., 1981). Stimulation of irritant receptors is also believed to be responsible for the occurrence of respiratory symptoms (Folinsbee et al., 1977b; McDonnell et al., 1983) and for alterations in ventilatory control (Folinsbee et al., 1975; Adams et al., 1981; McDonnell et al., 1983).

Unless measured at absolute lung volumes, decrements in forced expiratory flows (e.g., $FEV_{1.0}$, $FEF_{25-75\%}$) are difficult to interpret. Surely, most of the decline in flow is related to reduced maximal expiratory position, while a smaller portion results from airway narrowing (Folinsbee et al., 1978; McDonnell et al., 1983). Airway narrowing, as indicated by increased airway resistance, probably results from either smooth-muscle contraction, mucosal edema, or secretion of mucus. These can be initiated by vagally mediated reflexes from irritant receptor stimulation, by the interaction of an endogenous or exogenous substance with the vagal efferent pathway, or by the direct action of O_3 (or an O_3-induced, locally released substance) on smooth muscle or mucosa (Folinsbee et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). While it is possible that stimulation of airway receptors is the mechanism common to changes in airway resistance as well as in volumes and flows, McDonnell et al. (1983) have postulated the existence of more than one mechanism of action for O_3. They base this postulation on their observed lack of correlation between individual changes in FVC and SR_{aw} and on differences in dose-response curves for these two variables.

Two hypotheses have been proposed that are consistent with the observations of increased airway reactivity to histamine and methacholine following O_3 exposure (Holtzman et al., 1979). The first suggests that O_3 increases airway epithelial permeability, resulting in greater access of histamine and methacholine to bronchial smooth muscle and vagal sensory receptors. The second hypothesis suggests that O_3 or a byproduct of O_3 causes an increase in the number or the binding affinity of acetylcholine receptors on bronchial smooth muscle.

11.2.7 Pre-existing Disease

According to the National Health Interview Survey for 1979 (U.S. Department of Health and Human Services, 1981), there were an estimated 7,474,000 chronic bronchitics, 6,402,000 asthmatics, and 2,137,000 emphysematics in the United States. Although there is some overlap of about 1,000,000 in these three categories, it can be reasonably estimated that over 15,000,000 individuals experienced chronic respiratory conditions. That the effects of air pollutants on this large segment of our population have not received more attention by clinical investigators is surprising. In clinical studies that have been published, individuals with asthma or chronic obstructive lung disease (COLD) do not appear to be more sensitive to the effects of O_3 exposure than are normal subjects. Table 11-4 presents a summary of data from O_3 exposure in humans with pulmonary disease.

Linn et al. (1978) assessed pulmonary and biochemical responses of 22 asthmatics (minimal asthma to moderately severe chronic airway obstruction with limited disability) to 2-hr exposures to clean air, sham O_3, and 392 µg/m^3 (0.20 ppm) O_3 with secondary stressors of heat (31°C, 35 percent rh) and intermittent light exercise ($\dot{V}_E$ = 2 x resting $\dot{V}_E$). Subjects continued the use of appropriate medication throughout the study. Evaluation of responses was not made in relation to the severity of the disorder present in these patients. After baseline (zero O_3) studies were completed, subjects were exposed to filtered air, a sham (i.e., some O_3 was initially present in the exposure chamber), and a 392- to 490-µg/m^3 (0.20- to 0.25-ppm) O_3 condition (a 3-day control study was conducted over 3 days [0 ppm O_3] on 14 of these individuals). During each 2-hr exposure condition, subjects exercised for the first 15 min of each 30-min period. The exercise load was designed to double ventilatory volumes, but because of the relative physical condition of the subjects there was a wide variation in absolute $\dot{V}_E$ so that inhaled O_3 volume varied widely. Standard pulmonary function tests were performed pre- and post-exposure. No significant changes were noted except for a small change in TLC, which could have been explained by typical daily variations in this function. A slight increase in symptoms was also noted during O_3 exposures, but this increase was not statistically different from sham or control conditions. A spectrum of biochemical parameters was measured in blood obtained only post-exposure. The significant biochemical changes reported were small, and probably only represent the normally found individual and group variability seen in these parameters

TABLE 11-4. OZONE EXPOSURE IN SUBJECTS WITH PULMONARY DISEASE

Ozone concentration µg/m³	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and description of subjects	Reference
196 627 1960	0.1 0.32 1.0	MAST, NBKI	2 hr R	No effect on SR_{aw} and PaO_2; increased bronchial reactivity to ACh at 0.32 and 1.0 ppm in healthy subjects. SR_{aw} increased following ACh challenge in 2/3 COLD subjects at 0.1 ppm.	3 COLD 1 asthma 14 healthy	König et al., 1980
235	0.12	UV, NBKI	1 hr IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Decreased SaO_2 during exercise was observed.	25 COLD	Linn et al., 1982a Hackney et al., 1983
353 490	0.18 0.25	UV, NBKI	1 hr IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Group mean SaO_2 was not altered by O_3 exposure.	28 COLD	Linn et al., 1983
392	0.2	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No significant changes in pulmonary function. Small changes in blood biochemistry. Increase in symptom frequency reported.	22 asthma	Linn et al., 1978
392 588	0.2 0.3	CHEM, NBKI	2 hr IE (2R) for 7.5 min each half hour	No significant changes in pulmonary function or symptoms. SaO_2 decreased during exposure to 0.2 ppm.	13 COLD	Solic et al., 1982 Kehrl et al., 1983
490	0.25	CHEM, NBKI	2 hr R	No significant effect on pulmonary function. $\dot{V}_{50}$ decreased in approximately 1/3 of the subjects demonstrating selective sensitivity to O_3.	17 asthma	Silverman, 1979
784	0.4	UV/CHEM, UV	3 hr/day 6 days IE(4-5xR) for 15 min	FVC and FEV_3 decreased on the first of five consecutive exposure days and with re-exposure.	20 smokers with chronic bronchitis	Kulle et al., 1984

[a] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; UV = ultraviolet photometry.

[c] Activity level: R = rest; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min.

[d] See Glossary for the definition of symbols.

despite the investigators' suggestion that asthmatics may react biochemically at lower O_3 concentrations than nondiseased individuals.

Clinically documented asthmatics (16 years duration of asthma) were exposed either to filtered air or 490 $\mu g/m^3$ (0.25 ppm) of O_3 for 2 hr while quietly resting (Silverman, 1979). Pulmonary functions were measured in these 17 asthmatics before and after exposure. Additional measurements of expiratory flow-volume and ventilation were made at half-hour intervals during the 2-hr exposures. The objective of the study was to study asthmatics irrespective of the severity of their disease under the best degree of control that could be achieved, i.e., in their normal conditions of life. Paired t-tests showed no significant changes in lung-function measures related to O_3. However, some individual asthmatics did respond to O_3 exposure with a decrease in lung function and an exacerbation of symptoms. One group of six subjects had demonstrable decreases in function, but information concerning the stage and/or development of their asthma was inadequately addressed. Such information would have been extremely valuable in providing opportunities to study this more susceptible portion of the asthmatic population further.

Data from clinical studies have not indicated that asthmatics are more sensitive to O_3 than are normal subjects. However, the relative paucity of studies and some of the experimental design considerations (subject population, control of medication, exposure $\dot{V}_E$, appropriateness of pulmonary function measurements) in the two studies that have been published suggest that the responsiveness of asthmatics to O_3, relative to normal subjects, may be an unresolved issue. (This issue is treated in more detail in Chapter 13).

Linn et al. (1982a) studied 25 individuals (46 to 70 years old) with COLD; 12 percent were nonsmokers and the remainder were moderate to heavy smokers, with 11 individuals not smoking at this time. All had chronic respiratory symptoms with subnormal forced expiratory flow rates. Each subject underwent a control filtered air and a 235-$\mu g/m^3$ (0.12-ppm) O_3 exposure (randomized) for 1 hr. These subjects first exercised for 15 min, then rested for 15 min, then exercised for 15 min, and finally rested for 15 min. Exercise loads were designed to elevate $\dot{V}_E$ to 20 L/min (the physiological cost of this exercise to each of the wide variety of subjects was not identified). Pre- and post-exposure measurements of various pulmonary functions as well as arterial oxygen saturation (SaO_2) (Hewlett-Packard ear oximeter) were made. Only one pulmonary function test showed a significant difference related to O_3

(no tabulated data were presented). From pre-exposure values at rest (normal saturations) to mid-exposure values during exercise, mean SaO_2 increased by 0.65 ± 2.28 percent with purified air, but decreased by 0.65 ± 2.86 percent with O_3. This difference was significant. However, the decrement attributable to O_3 was near the limit of resolution of the oximeter and was detected by computer signal averaging; thus, its physiological and clinical significance is uncertain. Moreover, since many of the COLD subjects were smokers, interpreting changes in SaO_2 without knowing carboxyhemoglobin saturation (%COHb) is difficult. Preliminary reports of these same data have also been published (Hackney et al., 1983).

Solic et al. (1982) conducted a similar study of 13 COLD patients with the same age range (40 to 70 years) and with an approximately similar history as those used by Linn et al. (1982a). Their protocol consisted of two exposure days, one to filtered air (sham O_3) and one to 392 $\mu g/m^3$ (0.2 ppm) of O_3 in a randomized fashion. Subjects maintained their usual patterns of activity, drug use, etc., except for an imposition of no smoking for 1 hr prior to the baseline studies. During the 2-hr exposures, the subjects exercised for 7.5 min every half-hour at a load sufficient to increase $\dot{V}_E$ to 20 to 30 L/min and an oxygen uptake of $\sim$ 1 L/min. SaO_2 was measured during the last exercise period. Pulmonary function measurements were made before and after exposure, with FVC maneuvers also obtained at 1 hr of exposure. There was no statistically significant difference between the effects of air exposure versus O_3 exposure in any of the spirometric measurement values or symptoms. The only significant alteration resulting from O_3 exposure was found in SaO_2, where decrements were reported in 11 of 13 subjects. Arterial saturation was 95.3 percent on filtered-air days and 94.8 percent on O_3 days. Again, knowledge of %COHb is necessary to interpret these small changes in SaO_2 correctly.

Kehrl et al. (1983) presented further information on individuals with COLD. They restudied eight subjects from the group that Solic et al. (1982) had exposed to 392 $\mu g/m^3$ (0.2 ppm) of O_3. However, in this experiment the subjects were exposed to 588 $\mu g/m^3$ (0.3 ppm) of O_3. Kehrl et al. used a protocol similar to that used by Solic et al. Data presented consisted of measurements made during the 392-$\mu g/m^3$ (0.2-ppm) exposure, as well as new data obtained during the 588-$\mu g/m^3$ (0.3-ppm) exposures. The second exposure occurred 6 to 9 months later. No statistically significant O_3-induced changes in respiratory mechanics or symptoms were found in the COLD patients at either O_3

concentration. These observations are consistent with those obtained on normal individuals who exercised intermittently at similar levels of ventilation. Patients with COLD are exercise-limited, and studies that would induce higher ventilation are apparently not feasible. Therefore, it cannot be determined whether the failure to detect respiratory decrements could have been demonstrated if these individuals had been exercising more vigorously at 588 $\mu g/m^3$ (0.3 ppm) of O_3, inducing changes similar to those observed in normals at the same concentration.

Linn et al. (1983) presented data on 28 COLD patients exposed for 1 hr to 0, 353, and 490 $\mu g/m^3$ (0.0, 0.18, and 0.25 ppm) of O_3. These subjects exercised for the first and third 15-min periods and rested in the second and fourth periods. The exercise performed varied in intensity as did the corresponding $\dot{V}_E$. Forced expiratory function and symptoms measured before and after exposure were not influenced by the exposures, confirming other reports that these individuals do not respond to O_3 exposures even at levels of O_3 exceeding first-stage alert levels. In contrast to other reports of a small decrement in SaO_2, arterial oxygen saturation (ear oximeter) was not changed during the second exercise period and post-exposure. Medication and severity of disease may explain the divergent results previously obtained. Differences may also be related to the level of exercise and the resulting ventilation. As a consequence, these patients may have inhaled comparatively small doses of O_3.

In all these studies on COLD patients, a wide diversity of symptoms and ventilatory deficits was present. The common findings by Linn and Solic as to small changes in SaO_2 may be of some significance, although they were not confirmed in subsequent studies at higher O_3 concentrations. The exercise performed in these studies was of very low intensity, and results from O_3 exposures where COLD patients exercised at higher intensities may be of interest. However, the possibility that increased exercise intensity will be a relevant factor is unlikely; COLD patients in general cannot sustain much higher work outputs than used in these studies because of their limited maximal ventilation and possible cardiovascular insufficiency.

König et al. (1980) performed studies on 18 individuals, three of whom suffered from COLD and one of whom had extrinsic allergic asthma (bronchial symptom free). The bronchial reactivity test used ACh as the test substance. Specific airway resistance was measured in the patients after a 2-hr exposure to 196 $\mu g/m^3$ (0.1 ppm) of O_3 as well as on a sham-exposure day. In two of the three patients with COLD, increases in SR_{aw} of 37 and 39 percent were recorded after the O_3 exposure. The asthmatic patient was not affected by exposure to this level of O_3. Whether the results presented represent the response to a bronchial reactivity test immediately post-exposure or to the O_3 exposure is unclear. In addition, the small number of COLD subjects studied makes an adequate evaluation difficult.

Kulle et al. (1984) exposed 20 chronic bronchitic smokers for 3 hr to filtered air and 804 $\mu g/m^3$ (0.41 ppm) of O_3. Fifteen minutes of bicycle exercise at 100 W was performed during the second hour of exposure. Forced vital capacity and FEV_3 decreased significantly with exposure to O_3 compared to clean-air exposure; the decreases were small in magnitude (< 3 percent), and respiratory symptoms were mild.

11.2.8 Other Factors Affecting Pulmonary Responses to Ozone

11.2.8.1 Cigarette Smoking. Smokers have been studied as a population group having potentially altered sensitivity to oxidant exposures. Hazucha et al. (1973) and Bates and Hazucha (1973) reported the responses of 12 subjects divided by smoking history (six smokers and six nonsmokers) who were exposed to 725 and 1470 $\mu g/m^3$ (0.37 and 0.75 ppm) O_3. These young (23.6 ± 0.7 years old) individuals alternated 15 min of exercise at twice resting ventilation and 15 min of rest during the 2 hr of the test. Pulmonary-function measurements were made after each exercise period. The characteristic odor of O_3 was initially detectable by all subjects, but they were unaware of it after one-half hour. Symptoms of typical oxidant exposures were reported by all subjects at the termination of exposure. Decrements in FVC and $FEF_{25-75\%}$ were greater for nonsmokers after either O_3 exposure, whereas smokers exhibited greater decrements in $FEV_{1.0}$ and 50% V_{max}. Smokers exposed to 1470 $\mu g/m^3$ (0.75 ppm) of O_3 had a greater decrease in $FEF_{25-75\%}$ than did nonsmokers. The $FEF_{25-75\%}$ changes were much larger than the changes in $FEV_{1.0}$, regardless of O_3 concentration, exposure duration, and smoking habit. Smoking history (not given specifically) appeared to have different effects on the various pulmonary functions measured.

Kerr et al. (1975) exposed their subjects (10 smokers and 10 nonsmokers) to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for 6 hr, during which time the subjects exercised twice for 15 min each ($\dot{V}_E$ = 44 L). For the remainder of the exposure time the subjects were resting. Follow-up measurements were made 2 and 24 hr later. A control day on which subjects breathed filtered air preceded the O_3-exposure day. The 24-hr post-exposure study was conducted in filtered air. Variance analyses were used to interpret the data. In nonsmokers, significant decrements in ventilatory function were observed following O_3 exposure, being most prominent for FVC and FEV_3. Similar significant decrements were observed for FEV_1 and maximum mid-expiratory flow. No decrements were observed in mean spirometry values in smokers as a group; in fact, all tests disclosed some degree of improvement, with significance at the 5 percent level for MEF. A significant reduction in SG_{aw} was observed, for the most part in nonsmokers experiencing subjective symptoms. (All nonsmokers experienced one or more symptoms, while only 4 of 10 smokers had symptoms. These four smokers had been smoking for relatively short periods of time.)

Six subjects (three nonsmokers and three smokers of 20 cigarettes/day for 2 to 3 years) were studied by Kagawa and Tsuru (1979a). These subjects were exposed, no smoking on one day and smoking on another day, in either a filtered-air environment or one containing 588 $\mu g/m^3$ (0.3 ppm) of O_3. Two periods (10 min in duration) during the 2-hr exposure were devoted to smoking a cigarette. Smokers took one puff each minute (a total of 20 puffs) and nonsmokers took one puff every 2 min (a total of 10 puffs). Both groups reported a slight degree of dizziness and nausea after smoking. Measurements of SG_{aw} were obtained before and at the end of the first and second hours of exposure. Bronchial reactivity to an ACh challenge was determined pre- and post-exposure. The data presented in this report are minimal and sketchy, and statistical analyses are inadequate. One of the six subjects (a smoker) was a nonresponder to O_3. The remaining five responded in variable fashions, and direction of change could not be evaluated.

Kagawa (1983a) presented data on 5 smokers and 10 nonsmokers apparently exposed to 294 $\mu g/m^3$ (0.15 ppm) of O_3 for 2 hr to his standard intermittent rest-exercise regime. SG_{aw} was measured three times: at 1 and 2 hr during exposure and also at 1 hr post-exposure. Significant decreases were found during exposure, i.e., 4 percent at 1 hr and 10 percent at 2 hr in nonsmokers. No change from baseline occurred in the smokers. These data, which suggest significant differences in response between smokers and nonsmokers exposed to the low ambient level of 294 $\mu g/m^3$ (0.15 ppm) of O_3, were not presented in enough detail to permit independent evaluation of the findings.

DeLucia et al. (1983) reported that smokers (six men and six women) were relatively resistant to the oral inhalation of 588 $\mu g/m^3$ (0.3 ppm) of O_3. Few smokers detected the presence of O_3, whereas the majority of nonsmokers (six men and six women) experienced significant discomfort. Pulmonary function tests (FVC, FEV, and $FEV_{25-75\%}$) were made pre- and post-exposure (within 15 min). Overall, the decrements in pulmonary functions were significant and the authors attributed them to O_3. The relative insensitivity of smokers based on these three measurements was indicated by the decrements of 5.9 to 12.9 percent in nonsmokers, whereas smokers had 1.2 to 9.0 percent diminutions in these functions. Additional analyses of their pulmonary function data suggested that women nonsmokers were more sensitive to 588 $\mu g/m^3$ (0.3 ppm) of O_3 than women smokers. No apparent differences were noted for the men.

Thirty-two moderate or heavy smoking subjects (26 men and 6 women) were divided into four groups and exposed randomly to air alone, air plus smoking (2 cigarettes/hr), O_3 alone, and O_3 plus smoking (Shephard et al., 1983). Four O_3-exposure protocols were employed: 725 $\mu g/m^3$ (0.37 ppm) and 1470 $\mu g/m^3$ (0.75 ppm) in subjects at rest; and 980 $\mu g/m^3$ (0.50 ppm) and 1470 $\mu g/m^3$ (0.75 ppm) with the subjects exercising during the last 15 min of each half hour (the first 15 min of each period were at rest) for the 2-hr exposure. Carboxyhemoglobin was determined indirectly with the initial value being 1.61 percent. In nonsmoking days, COHb decreased, while on smoking days COHb increased by as much as 1.14 percent above the initial value. The increase in COHb was significantly lower on those days when smoking was conducted in an O_3 environment. Ozone exposure alone (no smoking during exposure) resulted in the typical and anticipated decreases in pulmonary functions (FVC, $FEV_{1.0}$, 25% $\dot{V}_{max}$, and 50% $\dot{V}_{max}$) as reported by others. However, the onset of these pulmonary changes was slower and the response less dramatic compared to data obtained on nonsmokers. The authors offered two explanations to account for the diminished response: (a) the presence of increased mucus secretion by these chronic smokers may have offered transient protection against O_3's irritant effect or (b) the sensitivity of the airway receptors may have been reduced by chronic smoking. The chronic effect of smoking induced a delay in the bronchial irritation response to O_3 exposure. There was no significant interaction between cigarette smoking and responses to O_3.

11.2.8.2 Age and Sex Differences. Although a number of controlled human exposures to O_3 have used both male and female subjects of varying ages, in most cases the studies have not been designed to determine age or sex differences. In fact, normal young males usually provide the subject population, and where subjects of differing age and sex are combined, the groups studied are often too small in number to test for potential differences reliably.

Adams et al. (1981) attempted to examine the effects of age on response to O_3 in a small number (n=8) of nonsmoking males varying in age from 22 to 46 years. Comparison of the mean change in pulmonary function between the three oldest subjects (33 to 46 years old) and the five youngest subjects (22 to 27 years old) revealed only small, inconsistent differences. Folinsbee et al. (1975), noting the lack of enough subjects for adequate subdivision, attempted to make sex comparisons in a group of 20 male and 8 female subjects exposed to O_3. No significant differences could be shown in either symptomology or physiological measurements between male and female subjects.

Horvath et al. (1979) studied eight male and seven female subjects exposed for 2 hr to 0, 490, 980, and 1470 $\mu g/m^3$ (0, 0.25, 0.50, and 0.75 ppm) of O_3. Forced expiratory function decreased immediately following exposure to 980 and 1470 $\mu g/m^3$ (0.50 and 0.75 ppm), with greater changes occurring at the highest O_3 concentration. The average decrements in $FEV_{1.0}$ were 3.1 and 10.8 percent, respectively, for men, compared to 8.6 and 19.0 percent for women. Although the data suggested that there may be potential sex differences in the extent of changes in lung function due to O_3 exposure, the results of an analysis of variance for sex differences were not presented.

Gliner et al. (1983) presented data on 8 male and 13 female subjects exposed for 2 hr on five consecutive days to 0, 392, 392, 392, and 823 or 980 $\mu g/m^3$ (0, 0.20, 0.20, 0.20, and 0.42 or 0.50 ppm) of O_3, respectively. During exposure the subjects alternated 15 min of rest with 15 min of exercise on a bicycle ergometer at loads sufficient to produce expired ventilations of approximately 30 L/min for men and 18 L/min for women. Forced expiratory measurements of FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ indicated that prior exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3 had no effect on functional decrements occurring after subsequent exposure to either 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3 on the fourth day (see Section 11.3). Although differences between men and women were reported for all three measurements, with men having expected larger expired volumes and flows, there were no pollutant interactions for six subjects, indicating that male and female subjects responded to O_3 in a similar fashion.

DeLucia et al. (1983) reported on 12 men and 12 women (equally divided by smoking history) exercising for 1 hr at 50 percent of their max $\dot{V}O_2$ while breathing 588 µg/m^2 (0.3 ppm) of O_3 through a mouthpiece. Minute ventilation for the men averaged 51 L/min and for the women 34.7 L/min. Women nonsmokers who did not inhale as much O_3 as nonsmoking men reported approximately a fourfold increase in symptoms, while smoking women had less severe symptomatic responses than smoking men. Although significant decrements in pulmonary function were found for FVC (6.9 percent), $FEV_{1.0}$ (7.9 percent), and $FEF_{25-75\%}$ (12.9 percent), there were no significant differences between the sexes. These investigators also found increases in f_B and decreases in V_T during exercise. These effects are similar to those reported by other investigators.

Gibbons and Adams (1984) recently reported the effects of exercising 10 young women for 1 hr at 66 percent of max $\dot{V}O_2$ while the women breathed 0, 297, or 594 µg/m^3 (0, 0.15, or 0.30 ppm) of O_3. Significant decrements in forced expiratory function were reported at 594 µg/m^3 (0.30 ppm) of O_3. Comparison of these effects with the results from male subjects previously studied by the authors (Adams et al., 1981) indicated that the women appeared to be more responsive to O_3 even though the men received a greater effective dose than the women. However, large individual variations in responsiveness were present in all subjects.

11.2.8.3 Environmental Conditions. Very few controlled human studies have addressed the potential influence environmental conditions such as heat or relative humidity (rh) may have on responses to O_3. In fact, most exposures have been performed under standard room temperature and humidity conditions (20-25°C, 45-50 percent rh). A series of studies by Hackney et al. (1975a,b,c; 1977a) and Linn et al. (1978) were conducted at a higher temperature and lower humidity (31°C, 35 percent rh) to simulate ambient environmental conditions during smog episodes in Los Angeles. No comparisons were made to the effects from O_3 exposure at standard environmental conditions in other controlled studies.

Folinsbee et al. (1977b) studied the effects of a 2-hr exposure to 980 µg/m^3 (0.5 ppm) of O_3 on 14 male subjects under four separate environmental conditions: (1) 25°C, 45 percent rh; (2) 31°C, 85 percent rh; (3) 35°C, 40 percent rh; and (4) 40°C, 50 percent rh. Wet bulb globe temperature (WBGT) equivalents were 64.4, 85.2, 80.0, and 92.0°F, respectively. The subjects exercised for 30 min at 40 percent of their max $\dot{V}O_2$ (Section 11.2.2 and

Figure 11-1). Decreases in vital capacity and maximum expiratory flow during O_3 exposure were most severe immediately after exercise. There was a trend for a greater reduction when heat stress and O_3 exposure were combined (WBGT=92.0°F), but this effect was only significant for FVC. In a similar study with eight subjects exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3 plus 940 $\mu g/m^3$ (0.5 ppm) of nitrogen dioxide (NO_2) (Folinsbee et al., 1981) (Section 11.6.3), the effects of heat and pollutant exposure on FVC were found to be no greater than additive. Part of the modification of O_3 effects by heat stress was attributed to increased ventilation since ventilatory volume and tidal volume increased significantly at the highest thermal condition studied (40°C, 50 percent rh).

More recently, Gibbons and Adams (1984) had 10 trained and heat-acclimated young women exercise for 1 hr at 66 percent of their maximum oxygen uptake while breathing either 0.0 $\mu g/m^3$ (0.0 ppm), 297 $\mu g/m^3$ (0.15 ppm), or 594 $\mu g/m^3$ (0.30 ppm) of O_3. These studies were conducted at two ambient conditions, i.e. 24° or 35°C. (Whether these are only dry bulb (db) temperatures or represent WBGT values is unclear, since humidity was not reported). No significant changes in any measured function were observed at 0 $\mu g/m^3$ (0.00 ppm) or 297 $\mu g/m^3$ (0.15 ppm) of O_3. Significant reductions in FVC, $FEV_{1.0}$, TLC, and $FEF_{25-75\%}$ ($P < 0.004$) were reported as a consequence of exercising at 594 $\mu g/m^3$ (0.30 ppm). Pre-post decrements in FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ in the 0.30 ppm, 24°C environment were 13.7, 16.5, and 19.4 percent respectively, compared to observed decrements of 19.9, 20.8, and 20.8 percent, respectively, in the 0.30-ppm O_3 and 35°C condition. Only FVC differed significantly between the two temperature conditions. Some subjects failed to complete the exercise period in 35°C and 0.30 ppm O_3, and one subject could not finish the exercise in 24°C and 0.30 ppm O_3. Subjects reported more subjective discomfort, (cough, pain on inspiration, throat tickle, dizziness, and nausea) as O_3 concentrations increased. No other effects were reported, although it was observed that O_3 (0.30 ppm) exposure and ambient high temperature induced an interactive effect on $\dot{V}_A$ and f_R.

11.3 PULMONARY EFFECTS FOLLOWING REPEATED EXPOSURE TO OZONE

Just as pulmonary function decrements following a single exposure to O_3 are well documented, several studies of the effects of repeated daily exposures to O_3 have also been completed (Table 11-5). In general, results from these studies indicate that with repeated daily exposures to O_3, decrements in pulmonary function are greatest on the second exposure day. Thereafter, on each succeeding day decrements are less than the day before, and on about the fifth exposure day small decrements or no changes are observed. Following a sequence of repeated daily exposures, there is a gradual time-related return of the susceptibility of pulmonary function to O_3 exposure similar to that observed prior to repeated exposures. Repeated daily exposure to a given low concentration of O_3 does not affect the magnitude of decrement in pulmonary function resulting from exposure at higher O_3 concentration.

All the reported studies of repeated responses to O_3 have used the term "adaptation" to describe the attenuation of decrements in pulmonary function that occurs. Unfortunately, since the initial report of such attenuation used adaptation, each succeeding author chose not to alter the continued use of this selected term. In the strict sense, adaptation implies that changes of a genetic nature have occurred as a result of natural selection processes, and as such, use of adaptation in the prior context is a misnomer.

Other terms (acclimation, acclimatization, desensitization, tolerance) have been recommended to replace adaptation and perhaps are more suitable. However, the correct use of any of these terms requires knowledge of (1) the physiological mechanisms involved in the original response, (2) which mechanisms are affected and how they are affected to alter the original response, and/or (3) whether the alteration of response is beneficial or detrimental to the organism. The present state of knowledge is such that we do not fully understand the physiological pathway(s) whereby decrements in pulmonary function are induced by O_3 exposure, and of course, the pathways involved in attenuating these decrements and how they are affected with repeated O_3 exposure are even less understood. Moreover, while attenuation of O_3-induced pulmonary function decrements appears to reflect protective mechanisms primarily directed against the acute and subchronic effects of the irritant, Bromberg and Hazucha (1982) have also speculated that this attenuation may reflect more severe effects of O_3 exposure, such as cell damage and death. Therefore, in the following discussion of specific studies, results will be presented without use of a specific term to describe observed phenomena generally. The use of response to imply pulmonary decrements resulting from O_3 exposure and changes in response or responsiveness of the subject to imply alterations in the magnitude of these decrements will be retained.

TABLE 11-5. CHANGES IN LUNG FUNCTION AFTER REPEATED DAILY EXPOSURE TO AMBIENT OZONE

Ozone Concentration µg/m³	ppm	Measurement[a,b] method	Exposure duration and activity[c]	No. of subjects	Percent change in $FEV_{1.0}$ on consecutive exposure days First	Second	Third	Fourth	Fifth	References
392	0.2	CHEM, NBKI	2 hr, IE(30)	10	+1.4	+2.7	-1.6	---	---	Folinsbee et al., 1980
392	0.2	UV, UV	2 hr, IE(18 & 30)	21	-3.0	-4.5	-1.1	---	---	Gliner et al., 1983
392	0.2	UV, UV	2 hr, IE(18 & 30)	9[d]	-8.7	-10.1	-3.2	---	---	Gliner et al., 1983
686	0.35	CHEM, NBKI	2 hr, IE(30)	10	-5.3	-5.0	-2.2	---	---	Folinsbee et al., 1980
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	14	-10.2	-14.0	-4.7	-3.2	-2.0	Farrell et al., 1979
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	13[e]	-9.2	-10.8	-5.3	-0.7	-1.0	Kulle et al., 1982b
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	11[e]	-8.8	-12.9	-4.1	-3.0	-1.6	Kulle et al., 1982b
784	0.4	UV, NBKI	2 hr, IE(2 x R)	7[f]	↑↑↑	↑	0			Dimeo et al., 1981
804	0.41	CHEM, NBKI & UV, UV	3 hr, IE(4-5 x R)	20[g]	-2.8	-0.9	0	-0.6	-1.1	Kulle et al., 1984
823	0.42	UV, UV	2 hr, IE(30)	24	-21.1	-26.4	-18.0	-6.3	-2.3	Horvath et al., 1981
921	0.47	UV, NBKI	2 hr, IE(3 x R)	11(7)[h]	-11.4	-22.9	-11.9	-4.3	---	Linn et al., 1982b
980	0.5	CHEM, NBKI	2 hr, IE(30)	8	-8.7	-16.5	-3.5	---	---	Folinsbee et al., 1980
980	0.5	CHEM, NBKI	2.5 hr, IE(2 x R)	6	-2.7	-4.9	-2.4	-0.7	---	Hackney et al., 1977a

[a] Measurement methods: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence, UV = ultraviolet photometry.

[b] Calibration methods: NBKI = neutral buffered potassium iodide; UV = UV photometry.

[c] Exposure duration and intermittent exercise (IE) intensity were variable; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] Subjects especially sensitive on prior exposure to 0.42 ppm O_3 as evidenced by a decrease in $FEV_{1.0}$ of more than 20%. These nine subjects are a subset of the total group of 21 individuals used in this study.

[e] Bronchial reactivity to a methacholine challenge was also studied.

[f] Bronchial reactivity to a histamine challenge (no data on $FEV_{1.0}$). SR_{aw} measured (↑). Note that on third day histamine response was equivalent to that observed in filtered air (see text).

[g] Subjects were smokers with chronic bronchitis.

[h] Seven subjects completed entire experiment.

Hackney et al. (1977a) performed the initial experiments that demonstrated that repeated daily exposures to O_3 resulted in augmented pulmonary function responses on the second exposure day and diminution of responses after several additional daily exposures. Six subjects who in prior studies had demonstrated responsiveness to O_3 were studied during a season of low smog to minimize potential effects from prior O_3 exposure. All but one subject had a history of allergies. They were exposed for approximately 2.5 hr to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for four consecutive days after one sham exposure. Ambient conditions in the chamber were 31°C db and 35 percent rh. During the first 2 hr, light exercise (of unknown level) was performed for 15 min every 30 min. The last half hour was used for pulmonary testing. Small decrements occurred in FVC and FEF_{75} and differed among the five test days. Additional statistical evaluation showed that these differences were related to the larger decrements in function observed on the second O_3 exposure day. Other pulmonary functions, i.e., total airway resistances (R_t) and nitrogen washout (ΔN_2), also improved on latter exposure days, but the differences were not statistically significant. The pattern of change clearly indicated that subjects had lesser degrees of pulmonary dysfunction by the third day of exposure, and these functions were nearly similar on day 4 to values found on the pre-exposure day to filtered air. In this small subject population, considerable variability in responses was noted (one subject with no history of allergies showed no pulmonary decrements, while another subject had a large reduction in FVC and FEV_1 and an increase in ΔN_2 on day 2 with a return of responses to near control levels on day 4).

Farrell et al. (1979) investigated the pulmonary responses of 14 healthy nonsmoking (10 men and 4 women) subjects to five consecutive, daily 3-hr exposures to filtered air or O_3. In the first week, subjects were studied in a filtered-air environment, followed in a second week with exposures to 784 $\mu g/m^3$ (0.4 ppm) of O_3. Pulmonary function (FVC, FEV_1, FEV_3, SG_{aw}, and FRC) was determined at the end of the 3-hr exposures. One bout of exercise ($\dot{V}_E$ measured on one subject = 44 L/min) was performed after 1.5 hr of exposure. Statistical evaluations used a repeated analysis of variance for significant differences between the control and O_3 exposure weeks, using each day of each exposure to make the comparisons. The analysis of variance showed that FVC, FEV_1, FEV_3, and SG_{aw} differed significantly between control and O_3 exposure weeks. No changes in FRC were found. In the O_3 exposure, SG_{aw} decreased significantly only on the first 2 days; this response was similar to air exposure day values on the last 3 days. The decrements were significantly greater on the second day than on the first. Decrements in $FEV_{1.0}$ and $FEV_{3.0}$ were substantial on the first day and increased on the second day of exposure. These decrements diminished to air exposure levels by the third day ($FEV_{3.0}$) and fourth day ($FEV_{1.0}$) of O_3 exposures. The severity of symptoms generally corresponded to the magnitude of pulmonary function changes. Symptoms were maximal on the first 2 days, decreasing thereafter with only one subject being symptomatic on the final day of exposure to O_3. Reporting of symptoms was maximal on the second O_3 day. These investigators noted that five consecutive days of exposure (10 subjects) to 588 $\mu g/m^3$ (0.3 ppm) of O_3 failed to induce significant changes in FVC or SG_{aw}, implying that measurable changes are likely to occur in pulmonary function at O_3 concentrations between 588 and 784 $\mu g/m^3$ (0.30 and 0.4 ppm) with 2 hr of exposure at these exercise levels.

Folinsbee et al. (1980) exposed healthy adult males for 2 hr in an environmental chamber at 35°C and 45 percent rh to filtered air on day 1, to O_3 on days 2 through 4, and to filtered air on day 5. Three groups of subjects were used, each exposed to a different concentration of O_3: group 1 (n=10), 392 $\mu g/m^3$ (0.20 ppm) of O_3; group 2 (n=10), 686 $\mu g/m^3$ (0.35 ppm) of O_3; group 3 (n=8), 980 $\mu g/m^3$ (0.50 ppm) of O_3. Subjects alternately rested and exercised at a $\dot{V}_E$ of 30 L/min for 15-min periods. There were no significant acute or cumulative effects of repeated exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3. With exposure to 686 $\mu g/m^3$ (0.35 ppm) of O_3, decrements in forced expiratory variables appeared on the first O_3 exposure day. Similar decrements occurred on the second O_3 exposure day, although there was no significant difference in responses observed on the first two exposure days. On the third day of exposure the pulmonary function changes were of lesser magnitude than on the first 2 days. In group 3, marked decrements in pulmonary function occurred ($FEV_{1.0}$ decreased 8.7 percent) after the first exposure to 980 $\mu g/m^3$ (0.50 ppm) of O_3; these decrements were even greater ($FEV_{1.0}$ decreased 16.5 percent) after the second O_3 exposure (Figure 11-5). While not totally abolished, an attenuation of these decrements ($FEV_{1.0}$ decreased 3.6 percent) was observed following the third O_3 exposure. The subjects claimed the most discomfort for the second O_3 exposure. Many noted marked reductions in symptoms on the third consecutive day of exposure to O_3. Two additional subjects were exposed to 980 $\mu g/m^3$ (0.50 ppm) of O_3 for four consecutive days. Although effects of O_3 on pulmonary

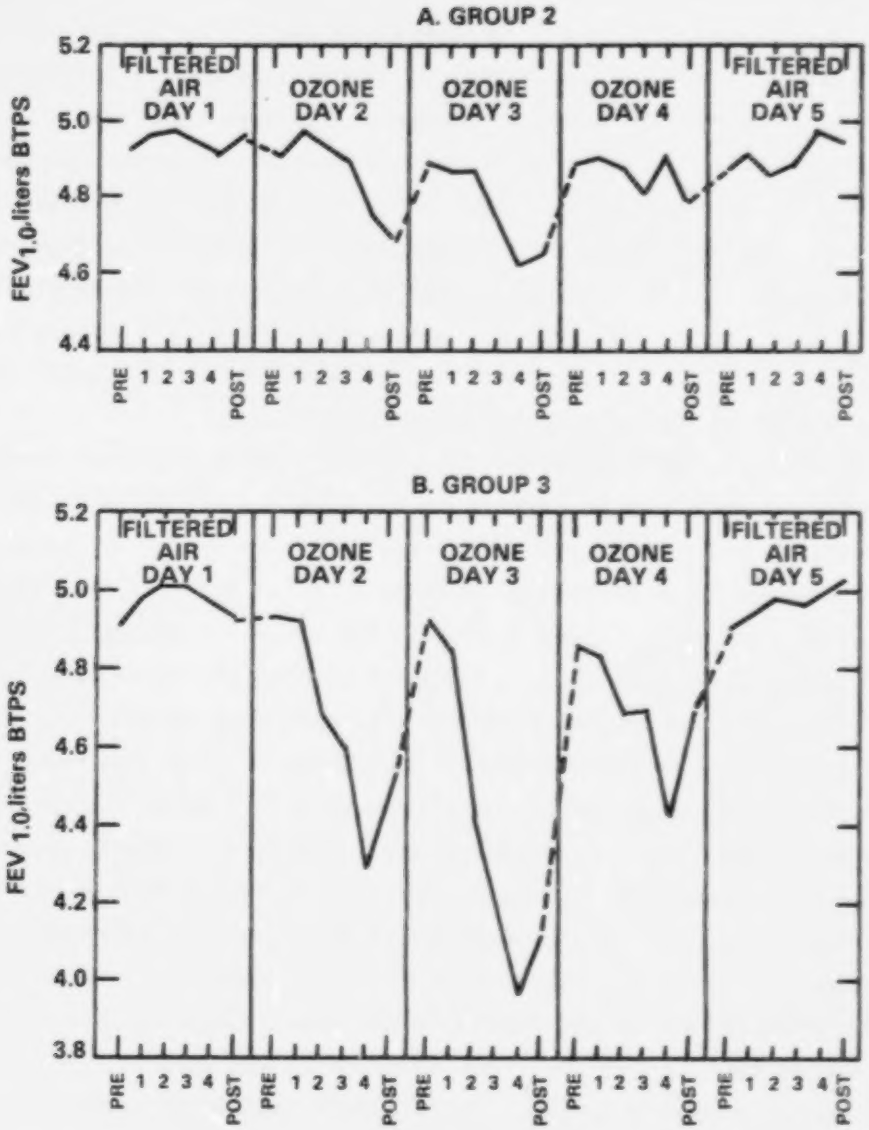

Figure 11-5. Forced expiratory volume in 1-sec ($FEV_{1.0}$) in two groups of subjects exposed to (A) 0.35 ppm ozone, and (B) 0.50 ppm ozone, for 3 successive days. Numbers on the abscissa represent successive half-hour periods of exposure.
Source: Folinsbee et al. (1980).

function were observed on the first two days of exposure, few effects were seen on the third day, and no effect was observed on the fourth day. The authors concluded that there were some short-term (2-day) cumulative effects of exposure to concentrations of O_3 that produced acute functional effects. This response period was followed by a period in which there was a marked lessening of the effect of O_3 on pulmonary function and on the subjective feelings of discomfort associated with exposure to O_3. The subjects for these studies represented a broad population mix in that some subjects had a prior history of respiratory difficulties, some essentially had no past respiratory history, and approximately two-thirds had prior experience with pollutant exposure.

Horvath et al. (1981) performed studies designed not only to determine further the influence of five consecutive days of exposure to 980 $\mu g/m^3$ (0.5 ppm), but to estimate the persistence of the attenuation of pulmonary responses. During the 125 min of exposure, 24 male subjects alternately rested and exercised ($\dot{V}_E$ = 30 L/min) for 15-min periods. Measurements of pulmonary functions were made daily pre- and post-exposure. A filtered-air exposure was conducted during the week prior to the O_3 exposures. Selected subjects were then randomly assigned to return after 6 to 7, 10 to 12, and 17 to 21 days for a single exposure to O_3. Ambient O_3 levels in the locations where the subjects lived seldom exceeded 235 $\mu g/m^3$ (0.12 ppm). The major pulmonary function measurements made and subjected to statistical analysis on these subjects were FVC, FEV_1, and $FEF_{25-75\%}$. Changes with time in all three measurements were similar and major emphasis was directed toward FEV_1 changes, since it was believed that this measurement would be commonly used in later epidemiological studies. Significant interaction effects occurred between the two within-subject factors (day of exposure and pre- and post-exposure change in FEV_1). The interaction resulted primarily from the post-exposure FEV_1 data, which revealed a "U"-shaped pattern across days during O_3 exposure. A significant decline appeared on day 1 (+1.7 to -63 percent, mean = -21 percent), and a greater significant decline appeared on day 2 (-26.4 percent). On day 3 the decrement in FEV_1 had returned to that observed on day 1, but it was still significantly greater than during room air exposure. The decrements in FEV_1 on days 4 and 5 had decreased significantly from day 3, but were still significantly larger than those with exposure to filtered air. Subjective symptoms followed a similar pattern, with subjects on the fifth day indicating that they had not perceived any O_3. Two subjects showed little attenuation of response to O_3, and one subject was not affected by the O_3 exposures. Subjects who were more responsive on the first day of exposure required more frequent daily exposure to attenuate response to O_3. Sixteen subjects were randomly requested to return for an additional O_3 exposure on days noted in Figure 11-6. Although the number of subjects in each repeat exposure was small, it was apparent that attenuation of response did not persist longer than 11 to 14 days, with some loss occurring within 6 to 7 days. In general, these authors made some interesting observations: (1) the time required to abolish pulmonary response to O_3 was directly related to the magnitude of the initial response; (2) the longer it took for attenuation of pulmonary response to O_3 to occur, the longer attenuation persisted; and (3) in some individuals, attenuation of pulmonary response to O_3 may persist up to 3 weeks. The mechanism responsible for attenuation of response was not elucidated, although two mechanisms were postulated, i.e., diminished irritant receptor sensitivity and increased airway mucus production.

Linn et al. (1982b) also studied the persistence of the attenuation of pulmonary responses that occurs with repeated daily exposures to O_3. Initially, 11 selected subjects, known to have previously exhibited pulmonary decrements in response to O_3 exposure, were exposed for 2 hr daily for four consecutive days to 921 $\mu g/m^3$ (0.47 ppm) O_3. Exposure consisted of alternating 15-min periods of moderate exercise ($\dot{V}_E$ = 3 x resting $\dot{V}_E$) and rest. An exposure to filtered air, under otherwise equivalent conditions, was conducted on the day prior to the first O_3 exposure. The pattern of change in pulmonary response to O_3 was similar to that previously reported for repeated daily exposures. For example, while the initial exposure to filtered air produced essentially no change, on the first O_3 exposure day FEV_1 decreased 11 percent, with a further decline to 23 percent on the second day, returning to approximately 11 percent on the third day. By the fourth day, the mean response was essentially equivalent to that observed with exposure to filtered air. While most of the subjects demonstrated attenuation of response (complete data sets on only seven subjects), the response of one subject, who may have had a persistent low-grade respiratory infection, never diminished. Two others showed relatively little response to the initial daily exposures, but showed some severe responses during follow-up exposures. This pattern was not to be unexpected, based on other studies demonstrating similar atypical responses.

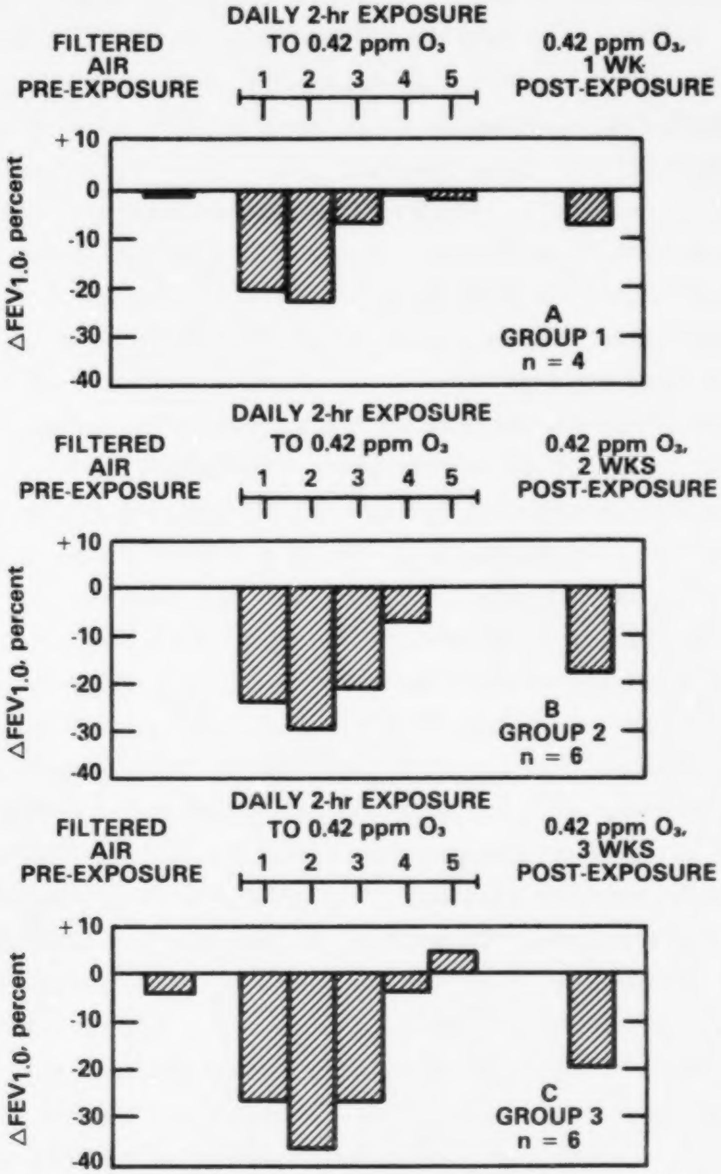

Figure 11-6. Percent change (pre-post) in 1-sec forced expiratory volume ($FEV_{1.0}$), as the result of a 2-hr exposure to 0.42 ppm ozone. Subjects were exposed to filtered air, to ozone for five consecutive days, and exposed to ozone again: (A) 1 wk later; (B) 2 wks later; and (C) 3 wks later. Source: Horvath et al. (1981).

To evaluate persistence of attenuated response, subjects repeated O_3 exposures under the above conditions 4 days after the repeated daily exposures and thereafter at 7-day intervals for five successive weeks. Four days after the repeated daily exposures, decrements in pulmonary function in response to O_3 exposure were identical to those observed after the first exposure to O_3 ($FEV_{1.0}$ decreased 11 percent). This magnitude of pulmonary decrement was also observed with subsequent O_3 exposures. Subjective symptoms generally paralleled lung-function studies, as had been observed in all previous studies. Since attenuation of pulmonary responses to O_3 may fail to develop or may be reversed quickly in the absence of frequent exposure, these authors questioned the importance of attenuation of response in the public health sense.

Following the design of an earlier protocol (Farrell et al., 1979), Kulle et al. (1982b) exposed 24 subjects (13 men and 11 women) for 3 hr on five consecutive days beginning on Monday to filtered air during week 1 and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 during week 2. During week 3, they exposed 11 subjects to filtered air on the first day and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the second day, while they exposed the remaining 13 subjects for 4 days to filtered air and then to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the fifth day. One hour prior to the end of each exposure, the subjects performed 15 min of exercise at 100 W ($\dot{V}_E$ = 4 to 5 times resting $\dot{V}_E$). Although the magnitude of decrement was notably less, the patterns of change in responses of FVC and FEV_1 were similar to those observed in previous studies, i.e., attenuation of response occurred during the 5 days of exposure. Attenuation of response was partially reversed 4 days after and not present 7 days after repeated daily exposures. These results agree with those of Linn et al. (1982b), but contrast to those of Horvath et al. (1981). Since the magnitude of decrements in pulmonary function (and also effective-exposure dose) was notably less in this study than in that of Horvath et al. (1981), these authors have suggested that the duration of attenuation of pulmonary response to O_3 may be related to the magnitude of decrement in response observed with the initial exposure to O_3.

Gliner et al. (1983) performed a study to determine whether daily repeated exposures to a low concentration of O_3 (392 $\mu g/m^3$; 0.20 ppm) would attenuate pulmonary function decrements resulting from exposure to a higher O_3 concentration (823 or 980 $\mu g/m^3$; 0.42 or 0.50 ppm). Twenty-one subjects (8 male, 13 female) were exposed for 2 hr on five consecutive days to filtered air (0.0 ppm O_3) on day 1, to 392 $\mu g/m^3$ (0.20 ppm) of O_3 on days 2, 3, and 4, and to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3 on day 5. For comparison, subjects who were exposed to 0.42 or 0.50 ppm of O_3 were exposed to the same O_3 concentration under identical conditions 12 weeks prior to or 6 to 8 weeks following the daily repeated exposures. During exposure, subjects alternately rested for 15 min and exercised for 15 min. Minute ventilation was 30 L/min for men and 18 L/min for women. Forced expiratory spirometry (FVC) was performed before and 5 min after the last exercise period. Analysis of continued results from all subjects indicated that three consecutive daily exposures to a low O_3 concentration (392 $\mu g/m^3$; 0.20 ppm) did not alter expected pulmonary function response to a subsequent exposure to a higher O_3 concentration (823 or 980 $\mu g/m^3$; 0.42 or 0.50 ppm).

Subjects were divided into two groups based on the magnitude of their response to the acute exposure to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) O_3. Nine subjects were considered to be responsive (FEV_1 decrements averaged 34 percent), and nine subjects were considered to be nonresponsive (FEV_1 decrements averaged less than 10 percent). Statistical analysis based on this grouping indicated that responsive subjects exhibited pulmonary function decrements after both their first and second, but not their third, exposure to 392 $\mu g/m^3$ (0.20 ppm); decreases in FVC and FEV_1 were about 9 percent. No significant effects of 392-$\mu g/m^3$ (0.20-ppm) O_3 exposure were found in the nonresponsive group. In both groups, repeated exposures to 0.20 ppm of O_3 had no influence on the subsequent response to the higher ambient O_3 exposure (823 or 980 $\mu g/m^3$; 0.42 or 0.50 ppm). Note that repeated exposures to the low O_3 concentration for only three consecutive days may have constituted insufficient total exposure (some combination of number of exposures, duration of exposures, $\dot{V}_E$, and O_3 concentration) to affect pulmonary function decrements resulting from exposure to higher O_3 concentrations. Additional studies, with consideration of total exposure and component variables, are needed to clarify this issue.

Haak et al. (1984) made a similar observation as Gliner et al. (1983) that exposure to a low effective dose of O_3 did not attenuate the response to a subsequent exposure at a higher effective dose of O_3. The pattern of pulmonary function decrements was evaluated following repeated daily 4-hr exposures to 784 $\mu g/m^3$ (0.40 ppm) of O_3 with two 15 min periods of heavy exercise ($\dot{V}_E$ = 57 L/min). As expected, pulmonary function decrements were greater on the second of five consecutive days of O_3 exposure; thereafter, the response was attenuated. Exposure at rest to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for two consecutive days had no effect on pulmonary function. Ozone exposure on the next two succeeding days with heavy exercise produced pulmonary function decrements similar to those observed previously in this study for the first two days of exposure to ozone.

Kulle et al. (1984) studied 20 smokers with chronic bronchitis over a 3-week period. The subjects breathed filtered air for 3 hr/day on Thursday and Friday of week 1 (control days), were exposed to 804 $\mu g/m^3$ (0.41 ppm) O_3 for 3 hr/day on Monday through Friday of week 2, and on week 3 breathed filtered air on Monday, then were re-exposed to 0.41 ppm O_3 on Tuesday. Bicycle ergometer exercise was performed at 2 hr of exposure at an intensity of 100 W for 15 min ($\dot{V}_E \sim$ 4-5 times resting). Spirometric measurements and recording of symptoms were made at the completion of all exposures. Small but significant decrements in FVC (2.6 percent) and FEV_3 (3.0 percent) occurred on the first day only of the 5-day repeated exposures as well as on re-exposure 4 days following cessation of the sequential exposures. Symptoms experienced were mild and did not predominate on any exposure days. These results indicate that individuals with chronic bronchitis also have attenuated responses with repeated exposures to O_3 that persist for no longer than 4 days. These results for smokers with chronic bronchitis contrast to those reported by the same investigators for normal nonsmoking subjects exposed under nearly identical conditions (Kulle et al., 1982b). Their normal subjects demonstrated larger decrements in FVC (8 percent) after the first and second exposures; thereafter the response was attenuated. This attenuation of response persisted beyond 4 days, and only with re-exposure 7 days after repeated exposures did significant decreases in FVC once again appear. These data also support the contention that persistence of an attenuated pulmonary response to O_3 is related to the magnitude of the initial response.

To determine if nonspecific bronchial reactivity is a factor involved in the attenuation of pulmonary responses to O_3, Dimeo et al. (1981) evaluated the effects of single and sequential O_3 exposures on the bronchomotor response to histamine. To determine the lowest concentration of O_3 that causes an increase in bronchial reactivity to histamine and to determine whether adaptation to this effect of O_3 develops with repeated exposures, they studied 19 healthy, nonsmoking normal adult subjects. Bronchial reactivity was assessed by measuring the rise in specific airway resistance (ΔSR_{aw}) produced by inhalation of 10 breaths of histamine aerosol (1.6-percent solution). In five subjects, bronchial reactivity was determined on four consecutive days without exposure to O_3 (group I). In seven other subjects (group II), bronchial reactivity was assessed on two consecutive days; subjects were exposed to 392 µg/m^3 (0.2 ppm) of O_3 on the third succeeding day and bronchial reactivity was determined after exposure. Seven additional subjects (group III) had bronchial reactivity assessed for two consecutive days and then again on the next three consecutive days after 2-hr exposures to 784 µg/m^3 (0.4 ppm) of O_3. Exposures consisted of alternating 15-min periods of rest and light exercise ($\dot{V}_E$ = 2x resting $\dot{V}_E$). Pre-exposure bronchial reactivity of the groups was the same, and no change in bronchial reactivity occurred in group I tested repeatedly but not exposed to O_3. An increase in ΔSR_{aw} provoked by histamine was noted after the first exposure to 784 µg/m^3 (0.4 ppm) but not to 392 µg/m^3 (0.2 ppm) of O_3. With three repeated 2-hr exposures to 0.4 ppm on consecutive days, the ΔSR_{aw} produced by histamine progressively decreased, returning to pre-exposure values after the third exposure. Their results indicated that with intermittent light exercise, the lowest concentration of ozone causing an increase in bronchial reactivity in healthy human subjects was between 392 and 784 µg/m^3 (0.2 and 0.4 ppm), and that attenuation of this effect of O_3 developed with repeated exposures. The lowest concentration of O_3 (identified in other studies using light or moderate exercise) that caused changes in symptoms, lung volumes, or airway resistance was also between 392 and 784 µg/m^3 (0.2 and 0.4 ppm), and the time course for the development of attenuation of these responses to O_3 was similar to that observed in this study. These authors propose that the appearance of symptoms, changes in pulmonary function, and the increase in bronchial reactivity may be related and caused by a change in the activity of afferent nerve endings in the airway epithelium.

Kulle et al. (1982b) also evaluated the effects of sequential O_3 exposure on bronchial reactivity. Nonsmoking subjects (n = 24) were exposed for 3 hr on five consecutive days each week to filtered air during week 1 and to 784 µg/m^3 (0.4 ppm) O_3 during week 2. During week 3, they exposed 11 subjects to filtered air on the first day and to 784 µg/m^3 (0.4 ppm) O_3 on the second day, while they exposed the remaining 13 subjects for 4 days to filtered air and then to 784 µg/m^3 (0.4 ppm) O_3 on the fifth day. A 15-min period of exercise at 100 W ($\dot{V}_E$ = 4 to 5 times resting $\dot{V}_E$) was performed 1 hr prior to the end of each exposure. After each exposure, a provocative bronchial challenge test was performed to determine bronchial reactivity to methacholine, defined as the log of the methacholine dose that provoked a 35 percent decrease in SG_{aw} from control. Bronchial reactivity to methacholine observed after exposure to O_3 on the iniital 2 to 3 days was significantly increased over that observed after exposure to filtered air, with no significant differences on the fourth and fifth days of exposure or with re-exposure 7 days later. The duration of the attenuated bronchial reactivity response was therefore much longer than that observed for FVC and $FEV_{1.0}$ in the same subjects, as noted earlier in this section.

An issue that merits attention is whether attenuated pulmonary responsiveness is beneficial or detrimental in that it may reflect the presence or development of underlying changes in neural responses or basic injury to lung tissues. Whether the attenuation of pulmonary function responses after repeated chamber exposures to O_3 is suggestive of reduced pulmonary responsiveness for chronically exposed residents of high-oxidant communities also remains unresolved.

11.4 EFFECTS OF OZONE ON VIGILANCE AND EXERCISE PERFORMANCE

Results from animal studies suggest that O_3 causes alterations in motor activity and behavior, but whether these responses result from odor perception, irritation, or a direct effect on the central nervous system (Chapter 10) is unknown. In fact, modification of the inclination to respond was suggested as possibly being more important than changes in the physiological capacity to perform simple or complex tasks. Very few human studies are available to help resolve this issue.

Henschler et al. (1960) determined the olfactory threshold in 10 to 14 male subjects exposed for 30 min to various O_3 concentrations. In a subgroup of 10 subjects, 9 individuals reported detection when the ambient concentration was as low as 39.2 $\mu g/m^3$ (0.02 ppm of O_3). Perception at this low level did not persist, being seldom noted after some 0.5 to 12 min of exposure. The odor of O_3 became more intense at concentrations of 98 $\mu g/m^3$ (0.05 ppm), according to 13 of 14 subjects tested, and it persisted for a longer period of time. No explanation was provided for the olfactory fatigue.

Eglite (1968) studied the effects of low O_3 concentrations on the olfactory threshold and on the electrical activity of the cerebral cortex. He found in his 20 subjects that the minimum perceptible concentration (olfactory threshold) for O_3 was between 0.015 and 0.04 mg/m^3 (0.008 and 0.02 ppm). The few subjects on whom electroencephalograms (EEGs) were recorded showed a 30 to 40 percent reduction of cerebral electrical activity during 3 min of exposure to 0.02 mg/m^3 (0.01 ppm) of O_3. The data are presented inadequately and can be considered only suggestive.

Gliner et al. (1979) determined the effects of 2-hr exposures to 0.0, 490, 980, or 1470 μg/m^3 (0.0, 0.25, 0.50, or 0.75 ppm) of O_3 on sustained visual and auditory attention tasks (vigilance performance). Eight male and seven female subjects performed tasks consisting of judging and responding to a series of 1-s light pulses which appeared every 3 s. The light pulses were either nonsignals (dimmer) or signals (brighter). When the ratio of signals to nonsignals was low (15 subjects), approximately 1 out of 30 performances was not altered regardless of the ambient level of O_3. However, when the ratio of signals was increased (five subjects), a deficit in performance beyond that of the normal vigilance decline was observed during the 1470-μg/m^3 (0.75-ppm) O_3 exposure. The results obtained were interpreted within the framework of an arousal hypothesis, suggesting that a high concentration of O_3 may produce overarousal.

Five individuals (four men, one woman) served as subjects (Gliner et al., 1980) in studies designed to evaluate the effects of O_3 on the electrical activity of the brain by monitoring the EEG during psychomotor performance. In the first experiment, a 2-hr visual sustained attention task was unaffected by exposure to filtered air or 1470 μg/m^3 (0.75 ppm) of O_3. The second experiment involved performing a divided-attention task, which combined a visual choice reaction time situation with an auditory sustained attention task. The O_3 concentrations were either 0.0, 588, or 1470 μg/m^3 (0.0, 0.3, or 0.75 ppm). Spectral and discriminant function analyses were performed on the EEGs collected during these studies. There was no clear discrimination between O_3 exposure and filtered air using the different parameters obtained from the EEG spectral analysis. Given the inability to obtain a discrimination between clean air and 1470 μg/m^3 (0.75 ppm) of O_3 using these techniques, EEG analysis does not appear to hold any promise as a quantitative method of assessing health effects of low-concentration (i.e., < 1484-μg/m^3; 0.3-ppm) O_3 exposure.

Mihevic et al. (1981) examined the effects of O_3 exposure (0.0, 588, 980 μg/m^3; 0.00, 0.30, and 0.50 ppm) in 14 young subjects who initially rested, then exercised for 40 min at heart rates of 124 to 130 beats/min, and finally rested for an additional 40 min. Pulmonary function measurements (FVC, FEV_1, and MEF_{25-75}) were made during rest periods and after exercise. The primary objective of the study was to examine the effects of exposure during exercise on perception of effort and to evaluate perceptual sensitivity to pulmonary responses. As expected, decrements in FVC, FEV_1, and MEF_{25-75} were significantly greater ($P < 0.01$) immediately after exercise than in the rest condition during either the 588- or 980-μg/m^3 (0.30- or 0.50-ppm) O_3 exposures. The work output remained the same in all conditions. However, the ratings of perceived exertion revealed that the subjects felt they were working harder or making a greater effort when exercising in the 0.50-ppm O_3 condition as compared to in-room air. The increased effort was perceived as a "central" effect (i.e., not related to effort or fatigue in the exercising muscles), which may suggest the perception of increased respiratory effort. The subjects also performed a test of magnitude estimation and production of inspired volume in which they either gave estimates of the percentage of increase in inspiratory capacity or attempted to produce breaths of a given size. From these tests an exponent was derived (by geometric regression analysis), which indicated the "perceptual sensitivity" to change in lung volume. The increase in this exponent following O_3 exposure (588, 980 μg/m^3; 0.30, 0.50 ppm) indicated that the subject's sensitivity to a change in lung volume was greater than it was following filtered-air exposure.

Early epidemiological studies on high school athletes (Chapter 12) provided suggestive information that exercise performance in an oxidant environment is depressed. The reports suggested that the effects may have been related to increased airway resistance or to the associated discomfort in breathing, thus limiting runners' motivation to perform at anticipated high levels. In controlled human studies, exercise performance has been evaluated during short-term maximal exercise or continuous exercise for periods up to 1 hr (Table 11-6). Folinsbee et al. (1977a) observed that maximal aerobic capacity (max $\dot{V}O_2$) decreased 10 percent, maximum attained work load was reduced by 10 percent, maximum ventilation (max $\dot{V}_E$) decreased 16 percent, and maximum heart rate dropped 6 percent after a 2-hr O_3 exposure (1470 μg/m^3; 0.75 ppm) with alternate rest and light exercise. A psychological impact related to the increased pain (difficulty) induced by maximal inspirations may have been the important factor in reduction in performance. Savin and Adams (1979) exposed nine exercising subjects for 30 min to 294 and 588 μg/m^3 (0.15 and 0.30 ppm) O_3 (mouthpiece inhalation). No effects on maximum work rate or max $\dot{V}O_2$ were found, although a significant reduction in max $\dot{V}_E$ was observed during the 588-μg/m^3 (0.30-ppm) exposure. Similarly, max $\dot{V}_{02}$ was not impaired in men and

TABLE 11-6. EFFECTS OF OZONE ON EXERCISE PERFORMANCE

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
$\mu g/m^3$	ppm					
294 588	0.15 0.30	UV, NBKI	30 min (mouthpiece) R & CE (8xR) @ progressive work loads to exhaustion	No effect on maximum work rate, anaerobic threshold, or pulmonary function; max $\dot{V}_E$ decreased with 0.30 ppm O_3.	9 male (runners)	Savin and Adams, 1979
392 686	0.20 0.35	UV, UV	1 hr (mouthpiece) IE (77.5) @ variable competitive intervals CE (77.5)	FVC, $FEV_{1.0}$, and FEF_{25-75} decreased, subjective symptoms increased with O_3 concentration at 68% max $\dot{V}O_2$; f_B increased and V_T decreased during CE; decreased during $\dot{V}O_2$, HR, $\dot{V}_E$, or $\dot{V}_A$. No exposure mode effect.	10 male (distance runners)	Adams and Schelegle, 1983
412	0.21	UV, UV	1 hr CE (81)	Decreases in FVC (6.9%), $FEV_{1.0}$ (14.8%), FEF_{25-75}% (18%), IC (11%), and MVV (17%) at 75% max $\dot{V}O_2$. Symptoms reported: laryngeal and tracheal irritation, soreness, and chest tightness on inspiration.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
490 980 1470	0.25 0.50 0.75	CHEM, NBKI	2 hr R (8) & CE @ progressive work loads to exhaustion	No effect on maximum exercise performance (max $\dot{V}O_2$, HR, and total performance time).	8 male 7 female	Horvath et al., 1979
1470	0.75	MAST, NBKI	2 hr IE (2.5xR) @ 15-min intervals	HR_{max}, $\dot{V}_E$, V_T, $\dot{V}O_{2max}$, and maximum workload all decreased. At maximum workload only, f_R decreased (45%) and V_T increased (29%).	13 male	Folinsbee et al., 1977a

[a] Measurement method: CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; UV = UV photometry.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] See Glossary for the definition of symbols.

women after 2-hr exposure and at-rest exposure to 0.0, 980, and 1470 μg/m^3 (0.00, 0.50, and 0.75 ppm) of O_3 (Horvath et al., 1979).

Six well-trained men and one well-trained woman (all except one male being a competitive distance cyclist) exercised continuously on a bicycle ergometer for 1 hr while breathing filtered air or 412 μg/m^3 (0.21 ppm) of O_3 (Folinsbee et al., 1984). They worked at 75 percent max $\dot{V}_{02}$ with mean minute ventilations of 81 L/min. As previously noted (Section 11.2.2), pulmonary function decrements as well as symptoms of laryngeal and/or tracheal irritation, chest soreness, and chest tightness were observed upon taking a deep breath. Anecdotal reports obtained from the cyclists supported the contention that performance may be impaired during competition at similar ambient O_3 levels.

Adams and Schelegle (1983) exposed 10 well-trained distance runners to 0.0, 392, and 686 μg/m^3 (0.0, 0.20, and 0.35 ppm) of O_3 while the runners exercised on a bicycle ergometer at work loads simulating either a 1-hr steady state training bout or a 30-min warmup followed immediately by a 30-min competitive bout. These exercise levels were of sufficient magnitude (68 percent of their max $\dot{V}_{02}$) to increase mean $\dot{V}_E$ to 80 L/min. In the last 30 min of the competitive exercise bout, minute ventilations were approximately 105 L/min. Subjective symptoms increased as a function of O_3 concentration for both continuous and competitive levels. In the competitive exposure, four runners (0.20 ppm) and nine runners (0.35 ppm) indicated that they could not have performed at their maximal levels. Three subjects were unable to complete either the training or competitive simulation exercise bouts at 0.35 ppm O_3, while a fourth failed to complete the competitive ride. As previously noted (Section 11.2.2), the high ventilation volumes resulted in marked pulmonary function impairment and altered ventilatory patterns. The decrements were the result of physiologically induced subjective limitations of performance due to respiratory discomfort. The authors found it necessary to reduce the 68 percent max $\dot{V}_{02}$ work load by some 20 to 30 percent in two of their subjects for them to complete the final 15 min (of the 30-min work time) in their competitive test.

Although studies on athletes (not all top-quality performers) have suggested some decrement in performance, too limited a data base is available at this time to provide judgmental decisions concerning the magnitude of such impairment. Subjective statements by individuals engaged in various sport activities indicate that these individuals may voluntarily limit strenuous exercise during high-oxidant concentrations. Several reviews on exercising subjects have appeared in the literature (Horvath, 1981; Folinsbee, 1981).

11.5 INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

An important issue is whether or not O_3 interacts with other pollutants to produce additive as well as greater than additive effects beyond those resulting from exposure to O_3 or the other pollutants alone. Also important to determine is whether no interactions occur when several pollutants are present simultaneously. Table 11-7 presents a summary of data on interactions between O_3 and other pollutants.

11.5.1 Ozone Plus Sulfates or Sulfuric Acid

Several studies have addressed the possible interaction between O_3 and sulfur compounds. Bates and Hazucha (1973) and Hazucha and Bates (1975) exposed eight volunteer male subjects to a mixture of 725 $\mu g/m^3$ (0.37 ppm) of O_3 and 0.37 ppm of sulfur dioxide (SO_2) for 2 hr. Temperature, humidity, concentrations, and particle sizes of ambient aerosols (if any) were not measured. Sulfur dioxide alone had no detectable effect on lung function, while exposure to O_3 alone resulted in decrements in pulmonary function. The combination of gases resulted in more severe respiratory symptoms and pulmonary changes than did O_3 alone. Using the maximal expiratory flow rate at 50 percent vital capacity as the most sensitive indicator, no change occurred after 2 hr of exposure to 0.37 ppm SO_2 alone. However, during exposure to 725 $\mu g/m^3$ (0.37 ppm) O_3 a 13 percent reduction occurred, while exposure to the mixture of 725 $\mu g/m^3$ (0.37 ppm) O_3 and 0.37 ppm SO_2 resulted in a reduction of 37 percent in this measure of pulmonary function. The effects resulting from O_3 and SO_2 in combination appeared in 30 min, in contrast to a 2-hr time lag for exposure to O_3 alone.

Bell et al. (1977) attempted to corroborate these studies using four normal and four O_3-sensitive subjects. They showed that the O_3 + SO_2 mixture had a greater detrimental effect on all pulmonary function measures than did O_3 alone. However, only one out of eight functional parameters showed statistically significant decrements when compared with O_3; $FEV_{1.0}$ decreased (4.7 percent) in the sensitive subjects. Four of the Hazucha and Bates (1975) study subjects were also studied by Bell et al. (1977). Two of these subjects had unusually large decrements in FVC (40 percent) and FEV_1 (44 percent) in the

TABLE 11-7. INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

Ozone concentration $\mu g/m^3$	ppm	Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
					A. $O_3 + SO_2$:		
294 393	0.15 0.15	O_3 SO_2	CHEM, NBKI EC	2 hr IE(25) @ 15-min intervals	SG_{aw} decreased; possible synergism is questionable. Statistical approach is weak.	6 male	Kagawa and Tsuru, 1979c
725 970	0.37 0.37	O_3 SO_2	MAST, NBKI EC	2 hr IE(2xR) @ 15-min intervals	Decrement in spirometric variables (FVC, MEFR 50%); synergism reported. Interpretation complicated by the probable presence of H_2SO_4.	8 male	Hazucha, 1973 Bates and Hazucha, 1973 Hazucha and Bates, 1975
725 970	0.37 0.37	O_3 SO_2	CHEM, NBKI FP	2 hr IE(2xR) @ 15-min intervals	Decreased forced expiratory function ($FEV_{1.0}$, FVC) relative to 0 exposure in combined group of normal and sensitive L.A. subjects more severe symptoms and greater decrement of $FEV_{1.0}$ in Montreal (5.2%) than L.A. sensitive (3.7%) subjects.	4 normal (L.A) 5 sensitive (L.A.) 4 normal (Montreal)	Bell et al., 1977
725 970 100	0.37 0.37	O_3 SO_2 H_2SO_4	UV, NBKI FP IC	2 hr IE(2xR) @ 15-min intervals	Small decreases in pulmonary function (FVC, $FEV_{1,2,3}$, MMFR, $\dot{V}_{max50}$, $\dot{V}_{max25}$) and slight increase in symptoms due primarily to O_3 alone; H_2SO_4 was 93% neutralized.	19 male	Kleinman et al., 1981
784 1048	0.4 0.4	O_3 SO_2	CHEM, NBKI FP	2 hr IE(30) @ 15-min intervals	Decreased forced expiratory function (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, $FEF_{50\%}$) following exposure to either O_3 or $O_3 + SO_2$; no differences observed between O_3 alone and $O_3 + SO_2$.	9 male	Bedi et al., 1979
784 1048	0.4 0.4	O_3 SO_2	CHEM, NBKI FP	2 hr IE(30) @ 15-min intervals	Observed decrement in pulmonary function ($FEV_{1.0}$, FVC, $FEF_{25-75\%}$, $FEF_{50\%}$, ERV, TLC) and increase in symptoms reflected changes due to O_3; no synergism was found.	8 male	Bedi et al., 1982
					B. $O_3 + H_2SO_4$:		
294 200	0.15	O_3 H_2SO_4	CHEM, NBKI IC	2 hr IE @15-min intervals	SGaw decreased; no interaction reported. Questionable statistics.	7 male	Kagawa, 1983a
588 100	0.3	O_3 H_2SO_4	MAST, NBKI & CHEM, NBKI TS	2 hr IE(35) for 15 min 4 hr IE(35) for 15 min	No significant O_3-related changes in pulmonary function or bronchial reactivity to methacholine. Bronchial reactivity decreased following a 4-hr exposure to H_2SO_4.	7 male 5 female	Kulle et al., 1982a

TABLE 11-7. INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS (continued)

Ozone concentration µg/m³	Ozone concentration ppm	Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
784 100 133 116 80	0.4	O_3 H_2SO_4 $(NH_4)_2SO_4$ NH_4HSO_4 NH_4NO_3	CHEM, NBKI	2-4 hr IE for two 15-min periods	Decrement in pulmonary function due to O_3 alone; more apparent after 4 hr than 2 hr; no interaction; recovery within 24 hr.	124 male (divided into 10 exposure groups)	Stacy et al., 1983
					C. O_3 + CO:		
588 115000	0.3 100.0	O_3 CO	MAST, BAKI IR	1 hr (mouth-piece) CE (51 for male and 34.7 for female subjects).	Decrement in pulmonary function due to O_3 alone: FVC, $FEV_{1.0}$ and $FEF_{25-75\%}$ decreased; f_B increased and V_T decreased with exercise.	12 male 12 female (equally divided by smoking history)	DeLucia et al., 1983
					D. O_3 + NO_2:		
196 9400	0.1 5.0	O_3 NO_2	CHEM, NBKI MAST (NO_2)	2 hr IE(2xR) @ 15-min intervals	Decreases in PaO_2 and increases in Raw due predominantly to NO_2 alone. No interaction reported.	12 male	von Nieding et al., 1977 von Nieding et al., 1979
294 200	0.15 0.15	O_3 NO_2	MAST, NBKI and CHEM, NBKI MAST, (NO_2) and CHEM, C	2 hr IE(25) @ 15-min intervals	SGaw decreased in 5/6 subjects during O_3 exposure, 3/6 subjects during NO_2 exposure, and in all subjects during the combined exposure. More than additive effect reported in 3/6 subjects. Coughing, chest pains, and chest discomfort related to O_3 exposure.	6 male	Kagawa and Tsuru, 1979b
490-980 560 35000	0.25-0.5 0.3 30.0	O_3 NO_2 CO	CHEM, NBKI CHEM, C IR	2-4 hr R & IE(2xR) @15-min intervals	No interaction reported. Changes observed in spirometry, lung mechanics, and small airway function in non-reactors (IE) and hyperreactors (R) at 0.5 ppm O_3.	16 normal and reactive subjects	Hackney et al., 1975a,b,c
980 940	0.5 0.5	O_3 NO_2	CHEM, NBKI CHEM, C	2 hr IE (40) for 30 min	Decreases in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$; ventilatory and metabolic variables were not changed; response was similar to that observed in O_3 exposure alone. Tightness in the chest and difficulty taking deep a breath was reported along with cough, substernal soreness, and shortness of breath.	8 male	Folinsbee et al., 1981

TABLE 11-7. INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS (continued)

Ozone concentration		Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
µg/m³	ppm						
980- 1372 940 1320	0.5- 0.7 0.5- 0.7	O_3 NO_2	MAST, NBKI and CHEM, NBKI MAST (NO_2) and CHEM, C	1 hr (mouthpiece) R	No significant changes in SGaw, $\dot{V}$max 50%, or $\dot{V}$max 25%.	5 male	Toyama et al., 1981
					E. $O_3 + NO_2 + SO_2$:		
49- 196 100- 9000 314 13000	0.025- 0.1 0.06- 5.0 0.12- 5.0	O_3 NO_2 SO_2	CHEM, NBKI MAST (NO_2) TS	2 hr IE (2xR) @ 15-min intervals	Decreases in PaO_2 and increases in Raw due to NO_2 alone at maximum concentrations; no effect at minimum concentrations. No interaction reported.	11 male	von Nieding et al., 1979
157 300 900	0.08 0.16 0.34	O_3 NO_2 SO_2	CHEM, NBKI and GS, CHEM CHEM, C	8 hr R	No effect on lung function, blood gases, or blood chemistry; questionable statistics.	15 male	Islam and Ulmer, 1979b
196 9400 13100	0.1 5.0 5.0	O_3 NO_2 SO_2	CHEM, NBKI GS, CHEM CHEM, C	2 hr IE	Random effects reported; questionable statistics; unknown exercise level.	24 male (divided into 3 age groups)	Islam and Ulmer, 1979a
294 280 393	0.15 0.15 0.15	O_3 NO_2 SO_2	CHEM, NBKI CHEM, C EC	2 hr IE @ 15-min intervals	Decreases in SG_{aw} due to O_3 alone. No interaction reported. Questionable statistics.	7 male	Kagawa, 1983a, 1983b

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[a] Pollutants studied for interactive effects: O_3 = ozone; SO_2 = sulfur dioxide; H_2SO_4 = sulfuric acid; $(NH_4)_2SO_4$ = ammonium sulfate; NH_4HSO_4 = ammonium bisulfate; NH_4NO_3 = ammonium nitrate; CO = carbon monoxide; NO_2 = nitrogen dioxide.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); MAST (NO_2) = microcoulometric NO_2 analyzer; CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry; GS-CHEM = gas solid chemiluminescence; IC = ion chromatography; EC = electrical conductivity SO_2 analyzer; FP = flame photometry SO_2 analyzer; TS = total sulfur analyzer; IR = infrared CO analyzer.

[c] Calibration method: NBKI = neutral buffered potassium iodide; BAKI = boric acid potassium iodide; C = colorimetric (Saltzman).

[d] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting $\dot{V}_E$.

[e] See Glossary for the definition of symbols.

[f] Part of a larger study of 231 subjects.

first study (Bates and Hazucha, 1973), while the other two had small but statistically significant decrements. None of the subjects responded in a similar manner in the Bell et al. (1977) study.

To determine why some of the Montreal subjects were less reactive to the SO_2-O_3 mixture when studied in Los Angeles compared to Montreal, Bell et al. (1977) compared exposure dynamics in the two chambers. Analysis of the design of the Montreal chamber and pollutant delivery system indicated that concentrated streams of SO_2 and O_3 could have reacted rapidly with each other and with ambient impurities like olefins, to form a large number of sulfuric acid (H_2SO_4) nuclei which grew by homogeneous condensation, coagulation, and absorption of ammonia (NH_3) during their 2-min average residence time in the chamber. A retrospective sampling of the aerosol composition used for the original SO_2-O_3 study in Montreal (Hazucha and Bates, 1975) using particle samplers and chemical analysis in the chamber showed that acid sulfate particles could have been 10- to 100-fold higher (100 to 200 $\mu g/m^3$), and thus might have been responsible for the synergistic effects observed. However, recent studies conducted by Kleinman et al. (1981) involving identical concentrations of SO_2 and O_3 showed that the presence of 100 $\mu g/m^3$ H_2SO_4 did not alter the response obtained with the SO_2-O_3 mixture alone. (See later discussion in this section.)

Bedi et al. (1979) exposed nine young healthy nonsmoking men (18 to 27 years old) to 784 $\mu g/m^3$ (0.4 ppm) O_3 and 0.4 ppm SO_2 singly and in combination for 2 hr in an inhalation chamber at 25°C and 45 percent rh. The subjects exercised intermittently for one-half of the exposure period. Pulmonary function was measured before, during, and after the exposure. Subjects exposed to filtered air or to 0.4 ppm SO_2 showed no significant changes in pulmonary function. When exposed to either O_3 or O_3 plus SO_2, the subjects showed statistically significant decreases in maximum expiratory flow ($FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$) and FVC. There were no significant differences between the effects of O_3 alone and the combination of O_3 + SO_2; thus, no synergistic effects were discernible in their subjects. Although particulate matter was not present in the inlet air, whether particles developed in the chamber at a later point is not known.

Chamber studies were also conducted by Kagawa and Tsuru (1979c), who exposed six subjects for 2 hr with intermittent exercise (50 W; i.e., ventilation of 25 L/min) for periods of 15 min of exercise separated by periods of 15 min of rest. The exposures were performed weekly in the following sequence: filtered air, 0.15 ppm of O_3; filtered air, 0.15 ppm of SO_2; filtered air; and finally 0.15 ppm of O_3 + 0.15 ppm of SO_2. Pulmonary function measurements were obtained prior to exposure, after 1 hr in the chamber, and after leaving the chamber. Although a number of pulmonary function tests were performed, change in SG_{aw} was used as the most sensitive test of change in function. They reported a significant decrease in five of the six young male subjects exposed to O_3 alone. In three of the subjects, they reported a significantly greater decrease in SG_{aw} after exposure to the combination of pollutants than with O_3 exposure alone. Two other subjects had similar decreases with either O_3 or O_3 + SO_2 exposure. Subjective symptoms of cough and bronchial irritation were reported to occur in subjects exposed to either O_3 or the O_3 + SO_2 combination. The authors suggested that the combined effect of the two gases on SG_{aw} is more than simply additive in some exercising subjects. This conclusion is questionable, however, because of the small number of subjects responding and the use of t-tests of paired observations to test the significance of pollutant-exposure effects. The statistical approach is weak despite the fact that the author selected a significance level of $P < 0.01$. The question of potential synergistic interaction between SO_2 and O_3 therefore remains unresolved by this study.

Bedi et al. (1982) attempted to explain the conflict of opinion over the cause of synergistic effects reported by Hazucha and Bates (1975) and Kagawa and Tsuru (1979c) for humans exposed to the combination of O_3 and SO_2. While intermittently exercising ($\dot{V}_E$ ~30 L/min), eight young adult nonsmoking males were randomly exposed on separate occasions for 2 hr to filtered air, 0.4 ppm SO_2, 748 $\mu g/m^3$ (0.4 ppm) of O_3, and 0.4 ppm of SO_2 plus 784 $\mu g/m^3$ (0.4 ppm) of O_3 at 35°C and 85 percent rh. No functional changes in $FEV_{1.0}$ occurred as a result of exposure to filtered air or 0.4 ppm of SO_2, but decreases in $FEV_{1.0}$ occurred following exposure to either 784 $\mu g/m^3$ (0.4 ppm) of O_3 (6.9 percent) or the combination of 784 $\mu g/m^3$ (0.4 ppm) of O_3 plus 0.4 ppm of SO_2 (7.4 percent). Thoracic gas volume (TGV) increased and $FEF_{50\%}$ decreased in the O_3 exposures, while FVC, $FEF_{25-75\%}$, $FEF_{50\%}$, ERV, and TLC all decreased in the O_3/SO_2 and O_3 exposures. However, no significant differences were found between the O_3 exposure and the O_3 plus SO_2 exposure. In this study, statistical analyses were performed using ANOVA procedures.

An analysis of the data obtained in the 1982 study and a prior study (Bedi et al., 1979) was also made using t-tests to compare data from these two studies with data obtained by Kagawa and Tsuru (1979c), who reported a synergistic effect consequent to exposure to 0.15 ppm of SO_2 and 294 $\mu g/m^3$ (0.15

ppm) of O_3 using t-tests. The experimental designs of the Bedi et al. and the Kagawa and Tsuru studies were essentially similar. Reanalysis of the Bedi et al. data using t-tests indicated that the SG_{aw} was not altered in the 25°C-45 percent rh environment but decreased 10.6 percent ($P < 0.05$) in the SO_2 exposure and 19 percent ($P < 0.01$) in O_3 plus SO_2 exposure in hot, wet conditions. These investigators concluded that in one sense they confirmed the findings (based on t-tests) of Kagawa and Tsuru, but under different conditions. This might suggest a small potential effect on SG_{aw}. They then stated, "Nonetheless, we believe that the use of a more stringent statistical approach provides for better analysis of collected data and that we are correct in stating that synergism had not occurred."

Few studies have been reported in which subjects were exposed to O_3 and H_2SO_4. Kagawa (1983a) summarized some results obtained on seven subjects intermittently resting and exercising during a 2-hr exposure to 294 $\mu g/m^3$ (0.15 ppm) of O_3 and 0.2 mg/m^3 of H_2SO_4. Using t-tests to analyze his data, he reported a highly significant ($P < 0.01$) decrease (10.2 percent) in SG_{aw}. However, not enough details are provided to allow adequate analysis.

Kleinman et al. (1981) conducted studies in which 19 volunteers with normal pulmonary function and no history of asthma were exposed on two separate days to clean air and to an atmospheric mixture containing O_3 (725 $\mu g/m^3$, 0.37 ppm), SO_2 (0.37 ppm), and H_2SO_4 aerosol (100 $\mu g/m^3$, MMAD = 0.5 μm; $\sigma_g = 3.0$). Chemical speciation data indicated that 93 percent of the H_2SO_4 aerosol had been partially neutralized to ammonium bisulfate. Additional data suggested that the acidity of the aerosol in the chamber decreased as a function of time during exposure, so that at the beginning of the exposures subjects were exposed to higher concentrations of H_2SO_4 than they were at the end of exposures. During this 2-hr period, the subjects alternately exercised for 15 min, at a level calibrated to double minute ventilation, and rested for 15 min. Statistical analysis of the group average data suggested that the mixture may have been slightly more irritating to the subjects than O_3 alone. A large percentage (13 of 19) of the subjects exhibited small decrements in pulmonary function following exposure to the mixture. The group average $FEV_{1.0}$ on the exposure day was depressed by 3.7 percent of the control value. However, the magnitudes of the $FEV_{1.0}$ changes were not higher than those observed in subjects exposed to O_3 alone (expected decreases of 2.8 percent). The authors concluded that the presence of H_2SO_4 aerosols did not substantially alter the irritability resulting from O_3-SO_2.

Stacy et al. (1983) studied 234 healthy men (18 to 40 years old) exposed for 4 hr to air, O_3, NO_2, or SO_2; to H_2SO_4, ammonium sulfate [$(NH_4)_2SO_4$], ammonium bisulfate (NH_4HSO_4), or ammonium nitrate (NH_4NO_3) aerosols; or to mixtures of these gaseous and aerosol pollutants. The subjects were divided into 20 groups so that each group contained 9 to 15 subjects. The exposure groups of interest were filtered air (n = 10); 784 $\mu g/m^3$ (0.4 ppm) of O_3 (n = 12); 100 $\mu g/m^3$ of H_2SO_4 (n = 11); 133 $\mu g/m^3$ of $(NH_4)_2SO_4$ (n = 13); 116 $\mu g/m^3$ of NH_4HSO_4 (n = 15); 80 $\mu g/m^3$ of NH_4NO_3 (n = 12); and the mixtures $O_3 + H_2SO_4$ (n = 13), $O_3 + (NH_4)_2SO_4$ (n = 15), $O_3 + NH_4HSO_4$ (n = 11), and $O_3 + NH_4NO_3$ (n = 12). Ambient conditions were 30°C db, 85 percent rh because of the need to maintain the aerosol particles in proper suspension. Two 15-min bouts of treadmill exercise were performed, one beginning at 100 min into the exposure and the second beginning at 220 min. Pre-exposure resting pulmonary functions were measured during a rest period. This battery of pulmonary function tests was also made some 5 to 6 min following the termination of the exercise and repeated 24 hr later. Unfortunately, the minute ventilations for the exercise periods were not reported. Data were analyzed by multivariate analyses of variance. All pulmonary functions (i.e., airway resistances, lung volumes, and flow rates) except ERV, FEV_1/FVC, and FRC showed a statistically significant effect of the gaseous pollutant (O_3). None of the particulates significantly altered pulmonary functions compared with the filtered-air exposure, and there was no indication of interaction between O_3 and the particulates. Only O_3 exposure affected pulmonary functions (16 of the 19 tests administered) and no significant interactions occurred with the sulfate aerosols. Interestingly, after 4 hr of exposure, SR_{aw} increased 27 percent with O_3; 41.7 percent with O_3/H_2SO_4; 28.5% with $O_3/(NH_4)_2SO_4$; and 34.7 percent with O_3/NH_4HSO_4. Although there was a trend toward increased O_3 effect in the presence of acid sulfates, it did not reach statistical significance. The reductions in FVC and FEF_{50} were approximately equivalent. At 24 hr post-exposure, all pulmonary values had returned to pre-exposure levels. Exposure to O_3 alone and with particles was associated with symptoms of irritation, viz. shortness of breath, coughing, and minor throat irritation. This comprehensive study confirms other observations that O_3 alone (at the levels of O_3 and sulfate aerosol stated) produced significant changes in pulmonary functions, albeit shortly after an exercise period. The data presented also suggested that O_3 induced greater changes at 4 hr than at 2 hr of exposure and that the changes were reversed within 24 hr.

Kulle et al. (1982a) studied the responses of 12 healthy nonsmokers (seven men, five women) exposed to O_3 and H_2SO_4 aerosols. Ozone concentrations were 588 μg/m^3 (0.3 ppm) and H_2SO_4 aerosol levels were 100 μg/m^3 (MMAD = 0.13 μm; σ_g = 2.4). These studies were conducted over a 3-week period; a 2-hr exposure to O_3, 4-hr exposure to H_2SO_4, and 2-hr exposure to O_3 were followed by a 4-hr exposure to H_2SO_4. The protocol followed in each of these weekly exposure regimes was day 1 - filtered air, day 2 - pollutant, and day 3 - filtered air. A methacholine aerosol challenge was made at the completion of each exposure day. Subjects were exercised for 15 min 1 hr prior to the completion of the exposure. The work load was 100 W at 60 rpm, with an assumed $\dot{V}_E$ of approximately 30 to 35 L. No discernible risk was apparent as a consequence of exposing the nonsmoking healthy young adults to O_3 followed by respirable H_2SO_4 aerosol. Bronchial reactivity decreased with H_2SO_4 aerosol exposure at a statistical level approaching significance ($0.05 < p < 0.10$). Pulmonary function changes (SG_{aw}, FVC, FEV_1, FEV_3, and bronchial reactivity to methacholine) following the O_3 exposure were not significant. However, some subjects did report typical symptoms observed in other O_3 exposures.

11.5.2 Ozone and Carbon Monoxide

DeLucia et al. (1983) reported the only study in which subjects were exposed to carbon monoxide (CO) and O_3. Subjects exercised at 50 percent max $\dot{V}_{O2}$ for 1 hr in the following ambient conditions: filtered air, 100 ppm of CO, 588 μg/m^3 (0.30 ppm) of O_3, and 100 ppm of CO plus 588 μg/m^3 (0.30 ppm) of O_3. These gas mixtures were administered directly, the subjects inhaling them orally for the entire exposure period. Twelve nonsmokers, six men and six women, and 12 smokers (not categorized as to smoking habits), equally divided by sex, served as subjects. There were relatively large differences in fitness between men and women as well as between smokers and nonsmokers, which could be responsible for some of the differences reported. Cardiorespiratory performance, heart rate, oxygen uptake, and minute ventilation were not substantially higher during exercise bouts where O_3 was present. All subjects exercised at 50 percent max $\dot{V}_{O2}$, equivalent to a mean $\dot{V}_E$ of 45.0 to 51.8 L/min for the men and 29.7 to 36.8 L/min for the women. The women, therefore, probably inhaled less O_3 than the men. Carboxyhemoglobin (COHb) levels attained at the end of the exercise period were similar for the two sexes, an average increase of 5.8 percent. Smokers' final COHb values were 9.3 ± 1.2 percent, compared with nonsmokers' levels of 7.3 ± 0.8 percent.

Based on the limited data available, exposure to CO and O_3 does not appear to result in any interactions. The effects noted appear to be related primarily to O_3.

11.5.3 Ozone and Nitrogen Dioxide

Studies describing the responses of subjects to the combination of these two pollutants are summarized in Table 11-7. Hackney et al. (1975a,b,c) and von Nieding et al. (1977, 1979) noted that no interactions were observed and that the pulmonary function changes were due to O_3 alone for the concentrations present. Kagawa and Tsuru (1979b) evaluated the reactions of six subjects (one smoker) to 294 µg/m³ (0.15 ppm) O_3 and 0.15 ppm NO_2, singly and in combination. They used the standard exposure time of 2 hr with alternating 15-min periods of rest and exercise at 50 W. SG_{aw} was determined prior to flow volume measurements and prior to and at two intervals during the exposure period. A fixed sequence of pollutant exposures was followed at weekly intervals, i.e., filtered air, 294 µg/m³ (0.15 ppm) of O_3, filtered air, 0.15 ppm of NO_2, filtered air, 0.15 ppm (O_3 + NO_2), and filtered air. Statistical analyses were by t-tests. Subjective symptoms were reported in some subjects only when O_3 was present. Significant decreases in SG_{aw} occurred in five of six subjects exposed to O_3, three of six subjects exposed to NO_2, and six of six subjects exposed to O_3 + NO_2.

Kagawa (1983a) briefly reported that under the conditions of his exposure (2 hr to 0.15 ppm O_3 + 0.15 ppm NO_2) SG_{aw}, $\dot{V}_{50\%}$, and VC decreased. However, no significant differences were observed between O_3 alone and the combination of O_3 + NO_2. Subjective symptoms were equivalent in both O_3 exposures.

Five subjects sitting in a body plethysmograph inhaled orally either filtered air, 0.7 ppm of NO_2, 1372 µg/m³ (0.7 ppm) of O_3, or 0.5 ppm of O_3 + 0.5 ppm of NO_2 for 1 hr (Toyama et al., 1981). Specific airway conductance and isovolume flows ($\dot{V}_{max\ 25\%}$ and $\dot{V}_{max\ 50\%}$) were measured before and at the end of exposure, and 1 hr later. No significant changes were observed for any of the ambient conditions and consequently no interactions could be detected.

Folinsbee et al. (1981) exposed eight healthy men for 2 hr to either filtered air or 980 µg/m³ (0.5 ppm) of O_3 plus 0.5 ppm of NO_2 in filtered air under four different environmental conditions: (1) 25°C, 45 percent rh; (2) 30°C, 85 percent rh; (3) 35°C, 40 percent rh; and (4) 40°C, 50 percent rh. Subjects rested for the first hour, exercised at a $\dot{V}_E$ of 40 L/min during the next half hour, and then rested for the final 30 min of exposure. Pulmonary function measurements were made prior to exposure, immediately after the exercise period, and again at the end of the 2-hr period. Significant decreases occurred in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$ during the O_3-NO_2 exposure. Ventilatory and metabolic variables, expired ventilation, oxygen uptake, tidal volume, and respiratory frequency were unaffected by O_3 and NO_2 exposure. Thermal conditions modified heart rate, ventilation, and FVC. Greater changes in pulmonary functions were seen in both groups following the exercise period with recovery of the decrements toward the pre-exposure value during the succeeding half hour of rest. In this study, no synergism or interaction between O_3 and NO_2 was observed over the entire range of ambient temperatures and relative humidities.

11.5.4 Ozone and Other Mixed Pollutants

Von Nieding et al. (1979) exposed 11 subjects to O_3, NO_2, and SO_2 singly and in various combinations. The subjects were exposed for 2 hr with 1 hr devoted to exercise (intermittent), which doubled their ventilation. The work periods were of 15 min duration alternating with 15-min periods at rest. In the actual exposure experiments, no significant alterations were observed for PO_2, PCO_2, and pH in arterialized capillary blood or in TGV. Arterial oxygen tension (PaO_2) was decreased (7 to 8 torr) by exposure to 5.0 ppm of NO_2 but was not further decreased following exposures to 5.0 ppm of NO_2 and 5.0 ppm of SO_2 or 5.0 ppm of NO_2, 5.0 ppm of SO_2 and 196 $\mu g/m^3$ (0.1 ppm) of O_3 or 5.0 ppm of NO_2 and 196 $\mu g/m^3$ (0.1 ppm) of O_3. Airway resistance increased significantly (0.5 to 1.5 cm $H_2O/L/s$) in the combination experiments to the same extent as in the exposures to NO_2 alone. In the 1-hr post-exposure period of the NO_2, SO_2, and O_3 experiment, R_t continued to increase. Subjects were also exposed to a mixture of 0.06 ppm NO_2, 0.12 ppm of SO_2, and 49 $\mu g/m^3$ (0.025 ppm) of O_3. No changes in any of the measured parameters were observed. These same subjects were challenged with 1-, 2-, and 3-percent aerosolized solutions of ACh following control (filtered-air) exposure and exposure to 5.0-ppm NO_2, 5.0-ppm SO_2, and 0.1-ppm O_3 mixture, as well as after the 0.06-ppm NO_2, 0.12-ppm SO_2, and 49-$\mu g/m^3$ (0.025-ppm) O_3 mixture exposures. Individual pollutant gases were not evaluated separately. ACh challenge caused the expected rise in airway resistance in the control study. Specific airway resistance (R_{aw} x TGV) was significantly greater following the combined pollutant exposures than in the control study.

In another study of simultaneous exposure to SO_2, NO_2, and O_3, three groups of eight subjects, each of different ages (<30, >49, and between 30 to 40 years) were exposed for 2 hr each day in a chamber on three successive days (Islam and Ulmer, 1979a). On the first day, subjects breathed filtered air and exercised intermittently (levels not given); on the second day they were exposed at rest to 5.0 ppm of SO_2, 5.0 ppm of NO_2, and 196 $\mu g/m^3$ (0.1 ppm) of O_3; and on the third day the environment was again 5.0 ppm of SO_2, 5.0 ppm of NO_2, and 196 $\mu g/m^3$ (0.1 ppm) of O_3, but the subjects exercised intermittently during the exposure. Statistical evaluation of data for the 11 lung-function test parameters and two blood gas parameters (PaO_2 and $PaCO_2$) was not reported. These measurements were made before exposure, immediately post-exposure, and 3 hr post-exposure. Individual variability was quite marked. The investigators concluded that no synergistic effects occurred in their healthy subjects. However, since they did not systematically expose these subjects to the individual components of their mixed pollutant environment, the conclusion can only be justified in that they apparently saw no consistent changes. There were some apparent changes in certain individuals related to exercise (unknown level) and age, but the data were not adequately presented or analyzed.

Islam and Ulmer (1979b) studied 15 young healthy males during chamber exposures to 0.9 mg/m^3 (0.34 ppm) SO_2, 0.3 mg/m^3 (0.16 ppm) NO_2, and 0.15 mg/m^3 (0.08 ppm) O_3. Ten subjects were exposed to 1 day of filtered air and four successive days of the gas mixture. Another group of five subjects was exposed for 4 days to the pollutant mixture followed by 1 day to filtered air. Each exposure lasted 8 hr. Following each exposure, the subjects were challenged by an ACh aerosol. Eight pulmonary function tests and four blood tests (PaO_2, $PaCO_2$, hemoglobin, and lactate dehydrogenase) were performed before and after the exposure. No impairments of lung functions, blood gases, or blood chemistry were found, but statistical analysis of the data was not reported. The authors reported that some of the subjects exhibited unusual responses.

11.6 EXTRAPULMONARY EFFECTS OF OZONE

The high oxidation potential of O_3 has led early investigators to suspect that the major damage from inhalation of this compound resulted from oxidation of labile components in biological systems to produce structural or biochemical lesions (Chapter 10). Initial studies by Buckley et al. (1975) suggested that

TABLE 11-8. HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
294 588	0.15 0.30	UV, NBKI	1 hr (mouthpiece) R (11) & CE (29, 43, 66)	No effect on NPSH, G-6-PD, 6-PG-D, GRase, Hb.	6 male	DeLucia and Adams, 1977
392	0.2	ND	0.5-1 hr	Spherocytosis.	e	Brinkman et al., 1964
392 490	0.2 0.25	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	Hb levels decreased. RBC enzymes: LDH increased, G-6-PD increased, AChE decreased. RBC fragility increased. All observed effects were stress related (heat).	20 male 2 female (asthma)	Linn et al., 1978
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	RBC fragility increased and serum vitamin E increased in Canadians only. RBC enzymes: AChE decreased in both groups.	2 male (Toronto) 2 female (Toronto) 3 male (L.A.) 1 female (L.A.)	Hackney et al., 1977b
784	0.4	CHEM, NBKI	4 hr IE for two 15-min periods	Mild suppression PHA-induced lymphocyte transformation. Questionable decrease in PMN phagocytosis and intracellular killing.	21 male	Peterson et al. (1978a,b)
784	0.4	CHEM, NBKI	4 hr R	No statistically significant depression in T-lymphocyte rosette formation. B-lymphocyte rosette formation with sensitized human erythrocytes was depressed immediately after but not 72 hr and 2 weeks after ozone exposure.	8 male	Savino et al., 1978
784	0.4	CHEM, NBKI	4 hr IE for two 15-min periods	No detectable cytogenetic effect.	26 male	McKenzie et al., 1977
784	0.4	CHEM, NBKI	2.25 hr IE (2xR) @ 15-min intervals	RBC fragility increased. RBC enzymes: AChE decreased; LDH increased in new arrivals. Serum glutathione reductase increased in new arrivals.	6 female (L.A.) 7 female (new arrival) 2 male (new arrival)	Hackney et al., 1976

TABLE 11-8. HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE (continued)

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
784	0.4	CHEM, NBKI	4 days 4 hr/day IE for two 15-min periods	RBC G-6-PD increased. Serum vitamin E increased. Complement C_3 increased.	74 male (divided into four exposure groups)	Chaney et al., 1979
784 1176	0.4 0.6	CHEM, NBKI	4 days 4 hr/day 2 hr IE for two 15-min periods	No detectable cytogenetic effects.	30 male	McKenzie et al., 1982
980	0.5	CHEM, NBKI	2.5 hr IE (2xR) @ 15-min intervals ± Vit E	No significant effects.	29 male and female	Hamburger et al., 1979
980	0.5	CHEM, NBKI	2.5 hr IE (2xR) @ 15-min intervals intervals	No significant effects.	9 male 28 female	Posin et al., 1979
980	0.5	CHEM, NBKI	2.75 hr IE (2xR) @ 15-min intervals	RBC fragility increased. RBC enzymes: LDH increased, G-6-PD increased, AChE decreased, GSH decreased. Serum: GSSRase decreased, vitamin E increased, lipid peroxidation levels increased.	7 male	Buckley et al., 1975
980	0.5	CHEM, NBKI	4 days 2.5 hr/day IE (2xR) @ 15-min intervals	Hb decreased after second exposure. RBC enzymes: GSH decreased after second exposure, 2,3-DPG increased and AChE decreased with successive exposures. Levels tended to stabilize with repeated exposure but did not return to control values.	6 male (Atopic)	Hackney et al., 1978
980	0.5	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	No effect on circulating lymphocytes.	31 male and female	Guerrero et al., 1979

TABLE 11-8. HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE (continued)

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
µg/m³	ppm					
980	0.5	MAST, NBKI	6-10 hr R	Frequency of chromatid aberrations increased immediately following exposure with a peak in number 2 weeks after exposure (not statistically significant); no change in number of chromosome aberrations.	6 male and female	Merz et al., 1975
1176	0.6	CHEM, NBKI	2 hr IE for two 15-min periods.	Suppression to PHA-induced lymphocyte transformation is questionable.	16 male	Peterson et al., 1981
1960	1.0	ND	10 min	Decreased rate of cutaneous HbO_2 desaturation	e	Brinkman and Lamberts, 1958

[a] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry; ND = not described.

[b] Calibration method: NBKI = neutral buffered potassium iodide.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or in multiples of resting ventilation.

[d] Abbreviations used: NPSH = nonprotein sulfhydryl; G-6-PD = glucose-6-phosphate dehydrogenase; 6-PG-D = 6-phosphogluconate dehydrogenase; GRase = glutathione reductase; Hb = hemoglobin; RBC = red blood cell; LDH = lactate dehydrogenase; AChE = acetylcholinesterase; PHA = phytohemagglutinin; GSSRase = glutathione reductase; GSH = reduced glutathione; 2,3-DPG = 2,3-diphosphoglycerate; HbO_2 = oxyhemoglobin; PMN = polymorphonuclear leukocytes.

[e] Details not given.

statistically significant changes ($P < 0.05$) occurred in erythrocytes and sera of seven young adult men following exposure to 980 $\mu g/m^3$ (0.50 ppm) of O_3 for 2.75 hr. Erythrocyte membrane fragility, glucose-6-phosphate dehydrogenase, and lactate dehydrogenase enzyme activities increased, while erythrocyte acetylcholinesterase activity and reduced gluthathione levels decreased. Serum gluthathione activity decreased significantly, while serum vitamin E and lipid peroxidation levels increased significantly. These changes were transitory and tended to disappear within several weeks. Although these changes were significant, that the alterations were such as to modify physiological systems or mechanisms is doubtful (see later reports in Table 11-8).

In the most comprehensive studies to date concerning the cytogenetic effects of inhaled O_3 in human subjects, McKenzie and co-workers have investigated both chromosome and chromatid aberrations (McKenzie et al., 1977) as well as sister chromatid exchange (SCE) frequencies (McKenzie, 1982). Blood samples from 26 normal male volunteers were collected before O_3 exposure; immediately after exposure; and 3 days, 2 weeks, and 4 weeks after exposure to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for 4 hr. Each subject served as his own control since pre-exposure blood samples were collected. A total of 13,000 human lymphocytes were analyzed cytogenetically. One hundred well-spread, intact metaphase plates were examined per subject per treatment time for chromosome number, breaks, gaps, deletions, fragments, rings, dicentrics, translocations, inversions, triradials, and quadriradials. The data indicated no apparent detectable cytogenetic effect resulting from exposure to O_3 under the conditions of the experiments.

In later studies, McKenzie (1982) investigated the SCE frequency, in addition to the number of chromosomal aberrations in peripheral lymphocytes of human subjects exposed to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for 4 hr on one day and on four consecutive days, or to 1176 $\mu g/m^3$ (0.6 ppm) for 2 hr. One hundred metaphases per blood sample per subject for chromosome aberrations, and 50 metaphases per blood sample per subject were analyzed for SCEs. Each study was conducted on 10 to 30 healthy, nonsmoking human subjects. No statistically significant differences were observed in the frequencies of numerical aberrations, structural aberrations, or SCEs between O_3 pre-exposure and post-exposure values. The nonsignificant differences were observed at all concentrations and durations tested, and in the multiple exposures as well as in the single O_3 exposures.

Chromosome and chromatid aberrations were investigated by Merz et al. (1975) in lymphocytes collected from subjects exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for 6 to 10 hr. Increases in the frequency of chromatid aberrations (achromatic lesions and chromatid deletions) were observed in lymphocytes after O_3 exposure, with a peak in the number of aberrations 2 weeks after exposure. No increase was observed in the number of chromosome aberrations. While these results suggest human genotoxicity after O_3 exposure, the results did not differ significantly from pre-O_3 chromatid aberration frequencies because of the small number (six) of subjects investigated.

Guerrero et al. (1979) exposed 31 male and female subjects to filtered air followed on a second day by 2-hr exposure to 980 $\mu g/m^3$ (0.5 ppm) of O_3. Subjects "lightly" exercised 15 min out of every 30 min. Blood samples were, unfortunately, obtained only at the termination of the exposures. An SCE analysis performed on the circulating lymphocytes showed no change in lymphocyte chromosomes in either condition. However, SCE analysis performed on diploid human fetal lung cells (WI-38) exposed to 0.0, 490, 1470, and 1960 $\mu g/m^3$ (0.0, 0.25, 0.75, and 1.00 ppm) of O_3 for 1 hr *in vitro* was shown to have a dose-related increase in SCEs. The investigators suggested that the lack of SCE changes in lymphocytes *in vivo* was attributable to the protective effect of serum and/or another agent.

Peterson and co-workers conducted three studies designed to evaluate the influence of O_3 exposures on leukocyte and lymphocyte function. In 1978, Peterson et al. (1978a) evaluated bactericidal and phagocytic rates in polymorphonuclear leukocytes from blood obtained before each exposure, 4 hr after exposure, as well as 3 and 14 days post-exposure. The 21 subjects were exposed for 4 hr to to 784 $\mu g/m^3$ (0.40 ppm) of O_3 at rest with the exception of two 15-min periods of exercise (700 kgm/min, resulting in a doubling of heart rate). The phagocytic rate and intracellular killing of respirable-size bacteria (*Staphylococcus epidermis*) was significantly reduced 72 hr after O_3 exposure. No significant effect on the phagocytic rate or intracellular killing was observed immediately after O_3 exposure, or at 2 weeks after O_3 exposure. The nadir of neutrophil function was observed at 72 hours after O_3 exposure. Since the neutrophil has an average lifespan of 6.5 hr, the mechanism by which O_3 produces an effect on the neutrophil at 72 hr is open to speculation. Ozone may produce indirect effects on neutrophils through toxicity to granulocytic stem cells, or by altering humoral factors that facilitate phagocytosis. A similar experimental protocol was used in a subsequent study on 11 subjects with the addition of a clean-air exposure with four subjects (Peterson et al., 1978b). The experimental description is confusing, because variable numbers of subjects were studied under different conditions. In the O_3 764-μg/m^3 (0.39-ppm) exposure (20 subjects), lymphocyte transformation responses to 2 μg/ml and 20 μg/ml of phytohemagglutinin (PHA) in cultures indicated significant ($P < 0.01$) suppression to 2 μg/ml of PHA in blood obtained immediately post-exposure but no effects with 20 μg/ml of PHA. The data, presented only in graphical form, suggested a wide variability in response, and consequently the significance of the observations may be minor. A third study was conducted by these investigators (Peterson et al., 1981) on 16 subjects exposed to 1176 μg/m^3 (0.6 ppm) of O_3. The protocol of rest, exercise, and blood sampling was similar to that used in their earlier studies except that one additional blood sample was obtained at least 1 to 2 months after the exposure. The relative frequency of lymphocytes in blood and the *in vitro* blastogenic response of the lymphocytes to PHA, concanavalin A (con A), poleweed mitogen (PWM), and *Candida albicans* were determined. In the second- and fourth-week blood samples, a significant ($P < 0.05$) reduced response to PHA was observed. No other alterations in function were observed. The significance of these findings remains somewhat tenuous.

Savino et al. (1978) observed that while peripheral blood T-lymphocyte rosette formation was unchanged following exposure of human subjects to 784 μg/m^3 (0.4 ppm) O_3 for 4 hr, B-lymphocyte rosette formation was significantly depressed. Rosette formation is an *in vitro* method that measures the binding of antigenic red blood cells with surface membrane sites on lymphocytes. Different antigenic red cells are used to distinguish T from B lymphocytes. A normal B-lymphocyte response was restored by 72 hr after O_3 exposure.

Biochemical parameters (erythrocyte fragility, hematocrit, hemoglobin, erythrocyte glutathione, acetylcholinesterase, glucose-6-phosphate dehydrogenase, and lactic acid dehydrogenase) were determined in blood obtained from subjects given either vitamin E or a placebo (Posin et al., 1979). Exposure conditions were filtered air on day 1 and 980 μg/m^3 (0.50 ppm) O_3 on day 2; 2 hr of exposure alternating with 15 min of exercise (double the resting minute ventilation) and 15 min of rest. Vitamin E intakes for nine or more weeks were 800 or 1600 IU. The number of subjects and the percent of men and women differed in each of the three studies conducted. No significant differences between the responses of the supplemented and placebo groups to the O_3

exposure were found for any of the parameters measured. Hamburger et al. (1979) obtained blood from the 29 subjects in one of the above three experiments (800 IU vitamin E and placebo). Blood was obtained before and after the 2-hr exposures to filtered air or 980 $\mu g/m^3$ (0.5 ppm) of O_3. No statistically significant change in erythrocyte agglutinability by concanavalin A was found.

In summary, the overall impression of available human data raises doubts that cellular damage or altered function to circulating cells occurs as a consequence of exposure to O_3 concentration under 980 to 1960 $\mu g/m^3$ (0.5 to 1.0 ppm).

11.7 PEROXYACETYL NITRATE

Subjects exposed to peroxyacetyl nitrate (PAN) complain of eye irritation, blurred vision, eye fatigue, and of the compound's distinctive odor. Smith (1965) had 32 young male subjects breathe orally 0.30 ppm PAN for 5 min at rest and continue to inhale this pollutant during a subsequent 5-min period of light exercise. Oxygen uptake during exercise was found to be statistically higher while breathing PAN than while breathing filtered air. These observations were not confirmed in subsequent studies (Table 11-9). Gliner et al. (1975) studied 10 young men (22 to 26 years of age) and nine older men (44 to 45 years) while they walked at 35 percent max $\dot{V}O_2$ for 3.5 hr of a 4-hr exposure to PAN. The ambient conditions in the chamber were either 25°C or 35°C dry bulb at 30 percent rh and the PAN concentration was either 0.0 or 0.24 ppm. Various measures of cardiorespiratory function were similar in both PAN and filtered-air exposures. A study of 16 older men (40 to 57 years) breathing 0.27 ppm PAN for 40 min found no changes in oxygen uptake during light work (Raven et al., 1974a).

The potential influence of PAN on $\dot{V}O_{2\ max}$ was determined in 20 young men who undertook a 20-min progressive modified Balke test while inhaling 0.27 ppm at ambient conditions of either 25°C (Raven et al. 1974b) or 37°C (Drinkwater et al., 1974). Total exposure time was 40 min. No alterations in cardiorespiratory functions or maximal aerobic capacity due to the pollutants were observed regardless of the ambient temperatures. Raven et al. (1974a) evaluated metabolic, cardiorespiratory, and body temperature responses of seven middle-aged (40 to 57 years) smokers and nine nonsmokers during tests of maximal aerobic power. Ambient conditions were 25°C or 35°C dry bulb and

TABLE 11-9. ACUTE HUMAN EXPOSURE TO PEROXYACETYL NITRATE

Concentration		Exposure duration and activity[a]	Observed effect(s)[b]	No. and sex of subjects	Reference
$\mu g/m^3$	ppm				
1187	0.24	4 hr IE (20-30) for 50 min of each hr.	FVC decreased 4% in 10 young subjects after exercise. No significant change in pulmonary function in nine middle-aged subjects. No interaction between exposure, temperature (25° & 35°C), or smoking habit.	19 male	Raven et al., 1976
1187	0.24	4 hr IE (20-30) for 50 min of each hr	No significant changes in submaximal work at 35% $\dot{V}O_{2max}$ in 10 young and nine middle-aged subjects. No interaction between exposure and temperature (25° & 35°C).	19 male	Gliner et al., 1975
1336	0.27	40 min IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in young nonsmokers (n = 10) or smokers (n = 10) during treadmill walk at 35°.	20 male	Drinkwater, 1974
1336	0.27	40 min IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in middle-aged nonsmokers (n = 9) or smokers (n = 7) during treadmill walk at 25°C and 35°C.	16 male	Raven et al., 1974a
1336	0.27	40 min (mouthpiece) IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in young nonsmokers (n = 10) or smokers (n = 10) during treadmill walk at 25°C.	20 male	Raven et al., 1974b
1484	0.30	10 min (mouthpiece) IE for 5 min	Oxygen uptake increased with exercise. Maximum expiratory flow rate decreased after exercise.	32 male	Smith, 1965

[a] Activity level: IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min.

[b] See Glossary for the definition of symbols.

25 percent rh. These subjects inhaled either filtered air or air containing 0.27 ppm PAN for 40 min. No effects of PAN were found. Effects related to age, smoking history, and ambient temperatures were as anticipated.

In his studies of young men orally inhaling 0.30 ppm PAN, Smith (1965) found a small reduction in MEFR following light exercise but no change in this function during resting exposures. Raven et al. (1976) observed a small but significant (4 to 7 percent) reduction in standing FVC in young men after 3.5 hr of light exercise (35 percent $\dot{V}O_{2\ max}$) during a 4-hr exposure to 0.24 ppm PAN.

The interaction of PAN and CO was also evaluated in the series of studies on healthy young and middle-aged men exercising on a treadmill (Raven et al., 1974a, 1974b; Drinkwater et al., 1974; Gliner et al., 1975). Both smokers and nonsmokers were exposed to 0.27 ppm PAN and 50 ppm CO. No interactions between CO and PAN were found. Metabolic, body temperature, and cardiorespiratory responses of healthy middle-aged men, nine smokers and seven nonsmokers, were obtained during tests of maximal aerobic power (max $\dot{V}_{02}$) at ambient temperatures of 25°C and 35°C, rh = 20 percent (Raven et al., 1974a). These subjects were randomly exposed for 40 min in an environmental chamber to each of four conditions, i.e., filtered air, 50 ppm CO, 0.27 ppm PAN, and a combination of 50 ppm of CO and 0.27 ppm of PAN. Carboxyhemoglobin was measured in these subjects. There was no significant change in maximal aerobic power related to the presence of these air pollutants, although total exercising time was lowered in the 25°C environment while exposed to CO. A decrement in max $\dot{V}_{02}$ was found in middle-aged smokers breathing 50 ppm of CO. Another study conducted under similar pollutant conditions at an ambient temperature of 35°C, 20 percent rh was carried out on 20 young male subjects (10 smokers and 10 nonsmokers) (Drinkwater et al., 1974). Maximal aerobic power was not affected by any pollutant condition. Exposure to CO was effective in reducing work time of the smokers. The same subjects were also involved in a study conducted at 25°C, 20 percent rh under similar pollutant conditions except that they inhaled the pollutants orally for 40 min (Raven et al., 1974b). Exposure to the two pollutants singly or in combination produced only minor, nonsignificant alterations in cardiorespiratory and temperature regulatory parameters. The influence of PAN and CO, singly or in combination, was evaluated in 10 young (22 to 26 years) and nine middle-aged (45 to 55 years) men performing submaximal work (35 percent max $\dot{V}_{02}$) for 210 min (Gliner et al., 1975). Five subjects in each age group were smokers. Studies were conducted at two different ambient temperatures, i.e., 25°C and 35°C, rh 30 percent. The pollutant concentrations were 0.25 ppm of PAN and 50 ppm of CO. Two physiological alterations were reported. Stroke volume decreased during long-term work, being enhanced in the higher ambient temperatures. Heart rate was significantly ($P < 0.05$) higher when exercise was being performed during the CO exposures. No other alterations were found in relation to the pollutants. There were no differences in response related to age.

11.8 SUMMARY

A number of important controlled studies discussed in this chapter have reported significant decrements in pulmonary function associated with O_3 exposure (Table 11-10). Results from studies of at-rest exposures to O_3 have demonstrated decrements in forced expiratory volumes and flows occurring at and above 980 $\mu g/m^3$ (0.5 ppm) of O_3 (Folinsbee et al., 1978; Horvath et al., 1979). Airway resistance is not clearly affected at these O_3 concentrations. At or below 588 $\mu g/m^3$ (0.3 ppm) of O_3, changes in pulmonary function do not occur during at rest exposure (Folinsbee et al., 1978), but the occurrence of some O_3 pulmonary symptoms has been suggested (König et al., 1980).

With moderate intermittent exercise at a $\dot{V}_E$ of 30 to 50 L/min, decrements in forced expiratory volumes and flows have been observed at and above 588 $\mu g/m^3$ (0.30 ppm) of O_3 (Folinsbee et al., 1978). With heavy intermittent exercise ($\dot{V}_E$ = 65 L/min), pulmonary symptoms are present and decrements in forced expiratory volumes and flows are suggested to occur following 2-hr exposures to 235 $\mu g/m^3$ (0.12 ppm) of O_3 (McDonnell et al., 1983). Symptoms are present and decrements in forced expiratory volumes and flows definitely occur at 353 to 470 $\mu g/m^3$ (0.18 to 0.24 ppm) of O_3 following 1 hr of continuous very heavy exercise at a $\dot{V}_E$ of 80 to 90 L/min (Adams and Schelegle, 1983; Folinsbee et al., 1984) and following 2 hr of intermittent heavy exercise at a $\dot{V}_E$ of 65 L/min (McDonnell et al., 1983). Airway resistance is only modestly affected even with heavy exercise while exposed at levels as high as 980 $\mu g/m^3$ (0.50 ppm) O_3 (Folinsbee et al., 1978; McDonnell et al., 1983). Increased f_R and decreased V_T, while maintaining the same $\dot{V}_E$, occur with prolonged heavy exercise when exposed at 392 to 470 $\mu g/m^3$ (0.20 to 0.24 ppm) of O_3 (McDonnell et al., 1983; Adams and Schelegle, 1983). While an increase in RV has been reported to result from exposure to 1470 $\mu g/m^3$ (0.75 ppm) of O_3 (Hazucha et al., 1973), changes in RV have not been observed following exposures to 980 $\mu g/m^3$

TABLE 11-10. SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE

Ozone[a] concentration		Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
μg/m³	ppm						
HEALTHY ADULT SUBJECTS AT REST							
627 1960	0.32 1.0	MAST, NBKI	2 hr	R	Specific airway resistance increased with acetylcholine challenge; subjective symptoms in 3/14 at 0.32 ppm and 8/14 at 1.0 ppm.	13 male 1 female	König et al., 1980
980	0.5	CHEM, NBKI	2 hr	R (10)	Decrement in forced expiratory volume and flow.	40 male (divided into four exposure groups)	Folinsbee et al., 1978
980 1470	0.50 0.75	CHEM, NBKI	2 hr	R (8)	Decrement in forced expiratory volume and flow.	8 male 7 female	Horvath et al., 1979
EXERCISING HEALTHY ADULTS							
235 353 470 588 784	0.12 0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr	IE (65) @ 15-min intervals	Decrement in forced expiratory volume and flow suggested at 0.12 ppm with larger decrements at $\geq$ 0.18 ppm; respiratory frequency and specific airway resistance increased and tidal volume decreased at $\geq$ 0.24 ppm; coughing reported at all concentrations, pain and shortness of breath at $\geq$ 0.24 ppm.	135 male (divided into six exposure groups)	McDonnell et al., 1983
392 686	0.20 0.35	UV, UV	1 hr (mouthpiece)	IE (77.5) @ variable competitive intervals CE (77.5)	Decrement in forced expiratory volume and flow with IE and CE; subjective symptoms increased with O_3 concentration and may limit performance; respiratory frequency increased and tidal volume decreased with CE.	10 male (distance runners)	Adams and Schelegle, 1983

TABLE 11-10. SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE (continued)

Ozone[a] concentration μg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
392 823 980	0.2 0.42 0.50	UV, UV	2 hr	IE (30 for male, 18 for female subjects) @ 15-min intervals	Repeated daily exposure to 0.2 ppm did not affect response at higher exposure concentrations (0.42 or 0.50 ppm); large intersubject variability but individual pulmonary function responses were highly reproducible.	8 male 13 female	Gliner et al., 1983
412	0.21	UV, UV	1 hr	CE (81)	Decrement in forced expiratory volume and flow; subjective symptoms may limit performance.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
588 980	0.3 0.5	CHEM, NBKI	2 hr	R (10), IE (31, 50, 67) @ 15-min intervals	Decrement in forced expiratory volume and flow; the magnitude of the change was related to O_3 concentration and V_E. Total lung capacity and inspiratory capacity decreased with IE (50, 67); no change in airway resistance or residual volume even at highest IE (67). No significant changes in pulmonary function were observed at 0.1 ppm.	40 male (divided into four exposure groups)	Folinsbee et al., 1978
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr	R (11) & IE (29) @ 15-min intervals	Good correlation between dose (concentration x $\dot{V}_E$) and decrement in forced expiratory volume and flow.	20 male 8 female (divided into six exposure groups)	Silverman et al., 1976
784	0.4	UV, NBKI	2 hr	IE (2xR) @ 15-min intervals	Specific airway resistance increased with histamine challenge; no changes were observed at concentrations of 0.2 ppm.	12 male 7 female (divided into three exposure groups)	Dimeo et al., 1981
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr	IE (4-5xR)	Decrement in forced expiratory volume was greatest on the 2nd of 5 exposure days; attenuated response by the 4th day of exposure.	10 male 4 female	Farrell et al., 1979

TABLE 11-10. SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE (continued)

Ozone[a] concentration µg/m³	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
784	0.4	CHEM, NBKI	3 hr	IE (4-5xR) for 15 min	Decrement in forced expiratory volume was greatest on the 2nd of 5 exposure days; attenuation of response occurred by the 5th day and persisted for 4 to 7 days. Enhanced bronchoreactivity with methacholine on the first 3 days; attenuation of response occurred by the 4th and 5th day and persisted for > 7 days.	13 male 11 female (divided into two exposure groups)	Kulle et al., 1982b
823	0.42	UV, UV	2 hr	IE (30)	Decrement in forced expiratory volume and flow greatest on the 2nd of 5 exposure days; attenuation of response occurred by the 5th day and persisted for < 14 days with considerable intersubject variability.	24 male	Horvath et al., 1981
921	0.47	UV, NBKI	2 hr	IE (3xR)	Decrement in forced expiratory volume and flow greatest on the 2nd of 4 exposure days; attenuation of response occurred by the 4th day and persisted for 4 days.	8 male 3 female	Linn et al., 1982b
1176	0.6	UV, NBKI	2 hr (noseclip)	IE (2xR) @ 15-min intervals	Specific airway resistance increased in 7 nonatopic subjects with histamine and methacholine and in 9 atopic subjects with histamine.	11 male 5 female (divided by history of atopy)	Holtzman et al., 1979
1470	0.75	MAST, NBKI	2 hr	IE (2xR) @ 15-min intervals	Decrements in spirometric variables (20%-55%); residual volume and closing capacity increased.	12 male	Mazucha et al., 1973

TABLE 11-10. SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE (continued)

Ozone[a] concentration µg/m³	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
ASTHMATICS							
392	0.2	CHEM, NBKI	2 hr	IE (2xR) @ 15-min intervals	No significant changes in pulmonary function. Small changes in blood biochemistry. Increase in symptom frequency reported.	20 male 2 female	Linn et al., 1978
490	0.25	CHEM, NBKI	2 hr	R	No significant changes in pulmonary function.	5 males 12 female	Silverman, 1979
SUBJECTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE							
235	0.12	UV, NBKI	1 hr	IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Decreased arterial oxygen saturation during exercise was observed.	18 male 7 female	Linn et al., 1982a
353 490	0.18 0.25	UV, NBKI	1 hr	IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Group mean arterial oxygen saturation was not altered by O_3 exposure.	15 male 13 female	Linn et al., 1983
392 588	0.2 0.3	CHEM, NBKI	2 hr	IE (28) for 7.5 min each half hour	No significant changes in pulmonary function or symptoms. Decreased arterial oxygen saturation during exposure to 0.2 ppm.	13 male	Solic et al., 1982 Kehrl et al., 1983
784	0.41	UV, UV	3 hr	IE (4-5xR) for 15 min	Small decreases in FVC and $FEV_{3.0}$.	17 male 3 female	Kulle et al., 1984

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[c] Calibration method: NBKI = neutral buffered potassium iodide; UV = ultraviolet photometry.

[d] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise; CE = continuous exercise.

(0.50 ppm) of O_3 or less, even with heavy exercise (Folinsbee et al., 1978). Decreases in TLC and IC have been observed to result from exposures to 980 $\mu g/m^3$ (0.50 ppm) of O_3 or less, with moderate and heavy exercise (Folinsbee et al., 1978).

Group mean decrements in pulmonary function can be predicted with some degree of accuracy when expressed as a function of effective dose of O_3, the simple product of O_3 concentration, $\dot{V}_E$, and exposure duration (Silverman et al., 1976). The relative contribution of these variables to pulmonary decrements is greater for O_3 concentration than for $\dot{V}_E$, which is greater than that for exposure duration. A greater degree of predictive accuracy is obtained if the contribution of these variables is appropriately weighted (Folinsbee et al., 1978). However, several additional factors make the interpretation of prediction equations more difficult. There is considerable intersubject variability in the magnitude of individual pulmonary function responses to O_3 (Horvath et al., 1981; Gliner et al, 1983; McDonnell et al., 1983). Individual responses to a given O_3 concentration have been shown to be quite reproducible (Gliner et al., 1983; McDonnell et al., 1984), indicating that some individuals are consistently more responsive to O_3 than are others. No information is available to account for these differences. Considering the great variability in individual pulmonary responses to O_3 exposure, prediction equations that only use some form of effective dose are not adequate for predicting individual responses to O_3.

In addition to overt changes in pulmonary function, enhanced nonspecific bronchial reactivity has been observed following exposures to O_3 concentrations as low as 588 $\mu g/m^3$ (0.3 ppm) (König et al., 1980). Exposure to 392 $\mu g/m^3$ (0.2 ppm) of O_3 with intermittent light exercise does not affect nonspecific bronchial reactivity (Dimeo et al., 1981).

Changes in forced expiratory volumes and flows resulting from O_3 exposure reflect reduced maximal inspiratory position (inspiratory capacity) (Folinsbee et al., 1978). These changes, as well as altered ventilatory control and the occurrence of respiratory symptoms, most likely result from sensitization or stimulation of airway irritant receptors (Folinsbee et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). The increased airways resistance observed following O_3 exposure is probably initiated by a similar mechanism; a modulation of this pathway, however, has been proposed to account for the lack of correlation between individual changes in SR_{aw} and FVC (McDonnell et al., 1983). The increased responsiveness of airways to histamine and methacholine following O_3 exposure most likely results from an O_3-induced increase in airways permeability or from an alteration of smooth muscle characteristics.

Decrements in pulmonary function were not observed for asthmatic subjects exposed for 2 hours at rest (Silverman, 1979) or with intermittent light exercise (Linn et al., 1978) to O_3 concentrations of 490 $\mu g/m^3$ (0.25 ppm) and less. Although this result indicates that asthmatics are not more sensitive to O_3 than are normal subjects, experimental-design considerations in reported studies suggest that this issue is still unresolved. For patients with COLD performing light to moderate intermittent exercise, no decrements in pulmonary function are observed for 1- and 2-hr exposures to O_3 concentrations of 588 $\mu g/m^3$ (0.30 ppm) and less (Linn et al., 1982a; Solic et al., 1982; Kehrl et al., 1983; Linn et al., 1983) and only small decreases in forced expiratory volume are observed for 3-hr exposures to 804 $\mu g/m^3$ (0.41 ppm) (Kulle et al., 1984). Small decreases in SaO_2 have also been observed, but interpretation of these decreases and their clinical significance is uncertain.

Many variables have not been adequately addressed in the available clinical data. Information derived from O_3 exposure of smokers and nonsmokers is sparse and somewhat inconsistent, perhaps partly because of undocumented variability in smoking histories. Although some degree of attenuation appears to occur in smokers, all current results should be interpreted with caution. Further and more precise studies are required to answer the complex problems associated with personal and ambient pollutant exposures. While a few studies have investigated sex differences, they have not conclusively demonstrated that men and women respond differently to O_3, and consideration of differences in pulmonary capacities have not been adequately taken into account. Environmental conditions such as heat and relative humidity may enhance subjective symptoms and physiological impairment following O_3 exposure, but the results so far indicate that the effects are no more than additive. Other variables such as seasonal effects and age, particularly the very young and the aged, need to be considered. In addition, there may be considerable interaction between these variables that may result in modification of interpretations made based on available information.

During repeated daily exposures to O_3, decrements in pulmonary function are greatest on the second exposure day (Farrell et al., 1979; Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982b); thereafter, pulmonary responsiveness to O_3 is attenuated with smaller decrements on each successive day than on the day before until the fourth or fifth exposure day when small decrements or no changes are observed. Following a sequence of repeated daily exposures, this attenuated pulmonary responsiveness persists for 4 (Kulle et al., 1982b; Linn et al., 1982b) to 7 (Horvath et al., 1981) days. Repeated daily exposures to a given low effective dose of O_3 does not affect the magnitude of decrements in pulmonary function resulting from exposure at a higher effective dose of O_3 (Gliner et al., 1983).

There is some evidence suggesting that exercise performance may be limited by exposure to O_3. Decrements in forced expiratory flow occurring with O_3 exposure during prolonged heavy exercise ($\dot{V}_E$ = 65 to 81 L/min) along with increased f_R and decreased V_T might be expected to produce ventilatory limitations at near maximal exercise. Results from exposure to ozone during high exercise levels (68 to 75 percent of max $\dot{V}O_2$) indicate that discomfort associated with maximal ventilation may be an important factor in limiting performance (Adams and Schelegle, 1983; Folinsbee et al., 1984). However, there is not enough data available to adequately address this issue.

No consistent cytogenetic or functional changes have been demonstrated in circulating cells from human subjects exposed to O_3 concentrations as high as 784 to 1176 $\mu g/m^3$ (0.4 to 0.6 ppm). Chromosome or chromatid aberrations would therefore be unlikely at lower O_3 levels. Limited data have indicated that O_3 can interfere with biochemical mechanisms in blood erythrocytes and sera but the physiological significance of these studies is questionable.

No significant enhancement of respiratory effects has been consistently demonstrated for combined exposures of O_3 with SO_2, NO_2, and sulfuric acid or particulate aerosols or with multiple combinations of these pollutants. Most of the available studies with other photochemical oxidants have been limited to a series of studies on the effects of peroxyacetyl nitrate (PAN) and carbon monoxide (CO) on healthy young and middle-aged males during intermittent exercise on a treadmill. No significant effects were observed at PAN concentrations of 0.25 to 0.27 ppm, which are higher than the daily maximum concentrations of PAN reported for relatively high oxidant areas (0.037 ppm). Two additional studies at 0.24 and 0.30 ppm of PAN suggested a possible limitation on forced expiratory volume and flow but there are not enough data to evaluate the significance of this effect. Further studies are also required on the more complex mix of pollutants found in the natural environment.

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12. FIELD AND EPIDEMIOLOGICAL STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

12.1 INTRODUCTION

This chapter critically assesses field and epidemiological studies of health effects linked to ambient air exposure to ozone and other photochemical oxidants. In order to characterize the nature and extent of such effects, the chapter (1) delineates types of health effects associated with ambient ozone or photochemical oxidant exposures; (2) attempts to determine quantitative relationships between exposures to these agents and observed effects; and (3) identifies population groups at greatest risk for such health effects. Studies of both acute and chronic exposure effects are discussed.

Many of the available epidemiological studies used exposure data or health endpoint measurements inadequate or unreliable for quantifying exposure-effect relationships. Also, results from these studies have often been confounded by factors such as variations in activity levels and time spent out of doors, cigarette smoking, poor hygiene, coexisting pollutants, weather, and socioeconomic status. Thus, selection of those studies thought to be most useful in attempting to derive health criteria for ozone or oxidants is of critical importance. To judge the relative scientific quality of epidemiological studies for standard-setting purposes, the following guidelines (as modified from U.S. Environmental Protection Agency, 1982) were set forth:

- The aerometric data are adequate to characterize geographic or temporal differences in pollutant exposures of study populations in the range(s) of pollutant concentrations evaluated.
- The study populations are well defined and allow for statistically adequate comparisons between groups or temporal analyses within groups.
- The health endpoints are scientifically plausible for the pollutant being studied; and the measurement methods are adequately characterized and implemented.
- The statistical analyses are appropriate and properly performed, using data subjected to adequate quality control.
- Potentially confounding or covarying factors are adequately controlled for or taken into account.

- The reported findings are internally coherent and biologically plausible.

For present purposes, greatest emphasis is placed here on discussion of studies that provide useful information on exposure-effect or exposure-response relationships associated with ambient air levels of ozone or photochemical oxidants likely to occur in the United States during the next 5 years. Accordingly, the following additional guidelines were used to select studies for detailed discussion: (1) the results provide information on quantitative relationships between health effects and ambient air ozone or oxidant concentrations with emphasis on concentrations less than or equal to 0.5 ppm (measurement methods and calibrations are reported when available) and (2) the report has been peer reviewed and is in the open literature or is in press. Some studies not meeting the above guidelines but considered to be sources of additional supportive information are also summarized below and their limitations noted.

12.2 FIELD STUDIES OF EFFECTS OF ACUTE EXPOSURE

Field studies of symptoms and pulmonary function combine features of controlled human exposure studies (Chapter 11) and epidemiological studies. These studies employ the more rigorous methods and better experimental control typical of controlled exposure studies with observations made in the field (Morris, 1970; Mausner and Bahn, 1974; American Thoracic Society, 1978; World Health Organization, 1983, 1984). Some attempt to mimic chamber conditions but include exposures of subjects to ambient air containing the pollutant(s) of interest as well as exposures to clean air as a control. They thus form a bridge or continuum between studies discussed in Chapter 11 and epidemiological studies assessed here.

12.2.1 Symptoms and Pulmonary Function in General Field Conditions

Some early studies of symptoms and pulmonary function under field oxidant exposure conditions were previously reviewed by the Environmental Protection Agency (1978). For example, Richardson and Middleton (1957, 1958) studied eye irritation in subjects under both air-filtration and nonfiltration conditions. They reported increased complaints to be associated with oxidant concentrations of 0.1 ppm, measured by the potassium iodide (KI) method, but not with nitrogen dioxide (NO_2) or suspended particles.

Balchum (1973) reported an expansion of a study by Remmers and Balchum (1965). Pulmonary function changes were observed in 15 patients with moderately severe chronic obstructive lung disease (COLD), who spent one week in a room without air filtration and a second week in a room with filtered air. In the unfiltered room, mean daily oxidants (KI method) averaged 0.11 ppm and ranged up to 0.2 ppm, but ranged from 0.02 to 0.03 ppm in the filtered room. Decreases in airway resistance and increases in arterial partial pressure of oxygen (PaO_2) appeared in both smokers and nonsmokers after 48 hours in filtered air, both when at rest and during exercise in about 75 percent of subjects. Reexamination of the 1965 data by Ury and Hexter (1969) showed airway resistance decreases to be more strongly correlated with oxidant concentrations than with either NO_2 or nitric oxide (NO) levels.

More recent field studies of pulmonary function have employed pre- and post-exercise function measurements (often used in controlled human exposure studies) in comparing the effects of short-term exposures to ambient air containing ozone and oxidants versus clean air (sham control) exposures. For example, in a series of studies carried out in a mobile laboratory, Linn and coworkers have shown pulmonary function decrements to be associated with exposure of Los Angeles area residents to ambient air containing ozone and other photochemical oxidants. The subject characteristics and experimental conditions employed in different studies by Linn and collaborators are summarized in Table 12-1 and associated pollutant levels in Table 12-2.

Linn et al. (1980, 1983) evaluated 30 asthmatic and 34 normal subjects exposed to ambient and purified air in a mobile laboratory in Duarte, CA (near Los Angeles) during two periods separated by 3 weeks. Only 5 subjects were smokers, and the two groups were similar in age, height, and sex ratio. Asthmatic subjects had heterogeneous disease characteristics, determined by questionnaire responses. Of the "normal" group, 25 subjects were considered allergic based on a history of upper respiratory allergy or reported undiagnosed wheeze which they called "allergic." Ozone, nitrogen oxides (NO_x), sulfur dioxide (SO_2), sulfates, and total suspended particulate matter (TSP) were monitored inside and outside the chamber at 5-min intervals, and validation studies were performed at the mobile laboratory. Measurements of O_3 by the ultraviolet (UV) method were calibrated against California Air Resources

TABLE 12-1. SUBJECT CHARACTERISTICS AND EXPERIMENTAL CONDITIONS OF THE MOBILE LABORATORY STUDIES

Subjects	1978[a]	1979[b]	1980[c]	1981[d]
Number	64	64	60	98
%Males	41	41	75	58
%Asthmatics	47	33	12	51
%Smokers	8	22	13	7
Age[e]	30±10	34±11	30±11	28±8
Height, cm[e]	170±10	170±12	173±15	172±9
Weight, kg[e]	70±14	69±16	69±10	67±11
Exercise	light intermittent	light intermittent	heavy continuous	heavy continuous
Exposure time	2 hr. (p.m.)	2 hr. (a.m.)	1 hr. (p.m.)	1 hr. (p.m.)
Location	Duarte	Hawthorne	Duarte	Duarte
Atmosphere	oxidant	primary pollutant	oxidant	oxidant

[a] Linn et al. (1980, 1983).

[b] Linn et al. (1982, 1983).

[c] Linn et al. (1983), Avol et al. (1983).

[d] Linn et al. (1983).

[e] Mean ± standard deviation.

TABLE 12-2. POLLUTANT LEVELS (MEAN ± S.D.) MONITORED INSIDE A MOBILE LABORATORY DURING AMBIENT AIR EXPOSURES

Subjects	1978[a]	1979[b]	1980[c]	1981[d]
O_3 (ppm)[e]	.174± .068	.022± .011	.165± .059	.156± .055
SO_2 (ppm)	.012± .003	.018± .099	.099± .005	.005± .033
NO_2 (ppm)	.069± .014	.056± .033	.050± .028	.062± .023
CO (ppm)	2.9 ± 1.1	1.6 ± 0.9	3.1 ± 2.0	2.2 ± 0.7
Particulate:				
Total (μg/m³)	182 ±42	112 ±45	227 ±76	166 ±52
SO_4^- (μg/m³)	16 ± 7	13 ± 6	17 ±12	9 ± 4
NO_3 (μg/m³)	[f]	19 ±10	22 ± 9	32 ±10

[a] Linn et al. (1980, 1983).

[b] Linn et al. (1982, 1983).

[c] Linn et al. (1983), Avol et al. (1983).

[d] Linn et al. (1983).

[e] Ultraviolet photometer calibration method.

[f] Measurements unsatisfactory due to artifact nitrate formation on filters.

Board (CARB) reference standards and corrected to those obtained by the KI method. The mobile laboratory has been described previously (Avol et al., 1979), as have the methods for studies of lung function. Lung function measures before and after exposure were compared by t-tests and nonparametric methods. Intermittent periods of exercise were combined with the exposure.

Ozone and particulate pollutants predominated in the ambient air mixture, as shown in Table 12-1 for the 1978 Duarte study. Ozone levels (corrected to the KI method) averaged 427 $\mu g/m^3$ (0.22 ppm) inside the mobile laboratory chamber and 509 $\mu g/m^3$ (0.26 ppm) outside the laboratory during ambient air exposures, and 7.8 $\mu g/m^3$ (0.004 ppm) during purified air exposures. Matching peak O_3 concentrations, respectively, were 498 ± 186 $\mu g/m^3$ (0.025 ± 0.10 ppm); 597 ± 217 $\mu g/m^3$ (0.31 ± 0.11 ppm); and 19 ± 17 $\mu g/m^3$ (0.01 ± 0.009 ppm). TSP levels averaged 182 $\mu g/m^3$ inside the chamber and 244 $\mu g/m^3$ outside the laboratory during ambient air exposures, but 49 $\mu g/m^3$ inside the chamber during purified-air exposures. Average NO_2, SO_2, CO, and sulfate levels inside the chamber were uniformly low during ambient-air exposures (as shown in Table 12-1) and were even lower during purified-air exposures (i.e., 0.015 ppm for NO_2; 0.009 ppm for SO_2; 2.8 ppm for CO; 0.9 ppm for sulfates). Gases were monitored continuously, alternatively inside and outside the mobile laboratory for 5-min periods. Particles were measured during testing inside and outside the laboratory. Temperature and humidity were controlled inside the laboratory.

During the exposure studies (Tuesday through Friday), four subjects (maximum) were tested sequentially in the morning at 15-min intervals, each first breathing purified air at rest followed by "pre-exposure" lung-function tests. Ambient-air chamber tests were performed in the early afternoon (after masking odors by a brief outside exposure). The ambient-air exposure period lasted 2 hr (and included exercise on bicycle ergometers for the first 15 min of each half-hour), followed by "post-exposure" lung function testing during continuing ambient-air exposure. Ergometer workloads ranged from 150 to 300 kg-m/min and were sufficient to approximately double the respiratory minute ventilation relative to resting level. The purified-air control study for each subject took place at least three weeks after the ambient-air exposure session, with identical procedures except for purified-air in place of the ambient. Note that Linn et al. (1980, 1983) also separately tested 12 healthy subjects from the project staff in order to validate various aspects of the study. The validation tests indicated insignificant variability in the measurement methods for healthy normal subjects.

In the main set of experiments, The asthmatic group experienced greater changes from baseline in residual volume (RV) and peak flow measurements with exercise than did the "normals," based on data adjusted for subject age, height, and weight. The magnitude of these changes did not correlate with age. Both groups showed similar changes in most of the other lung-function measurements. Regression analysis showed no significant associations of functional changes with TSP, total sulfate, total NH_3, or NO_2. Increasing O_3 was correlated with decreasing peak flow and 1-sec forced expiratory volume (FEV_1). No explanation was given for an association of increasing CO with increasing RV and with the slope of the alveolar plateau (SBNT). Increasing SO_2 was significantly associated with increasing RV and total lung capacity (TLC). In multiple regression analysis, O_3 was the variable contributing the most variation in FEV_1 and maximum expiratory flow ($\dot{V}_{max25\%}$), as well as in the FEV_1 normalized for forced vital capacity ($FEV_1/FVC\%$), TLC, and pulmonary resistance (R_t) in the normal/allergic group. Although other pollutant variables contributed to the observed effects, none did so consistently. Apart from O_3, functional changes on control days (intraindividual variability), smoking habits, and age appeared to explain the functional changes in normals/allergics during exposure. In asthmatics, all pollutant variables except TSP were significant in one or more analyses, but not all consistently. Asthmatics and normals/allergics also had significantly increased symptom scores during ambient air exposure sessions. This increase appeared to last later into the day in asthmatics but not in normals/ allergics (Figure 12-1).

Nine of 12 highly reactive subjects (four from the normal/allergic group and five asthmatics--a similar proportion from each group), who had experienced a fall in FEV_1 greater than 200 ml during ambient exposure (compared to purified-air exposure), underwent a controlled 2-hr exposure experiment at 392 $\mu g/m^3$ (0.2 ppm) with intermittent exercise (see Chapter 11). Among these nine reactive subjects, the mean FEV_1 change in the ambient exposure was -273 ± 196 ml (-7.8 ± 6.3 percent of pre-exposure). This change was significantly greater than the mean change of -72 ± 173 ml (3.1 ± 6.6 percent pre-exposure) in the control setting. The authors suggested that ambient exposures had greater effects than chamber exposures. Normal/allergic subjects in the validation studies showed similar findings in the exposure chambers compared to the outside ambient air when the levels were similar inside and out.

Linn et al. (1982, 1983) repeated the initial experiment (Linn et al., 1980) with 64 different subjects, ages 18 to 55, at a different location

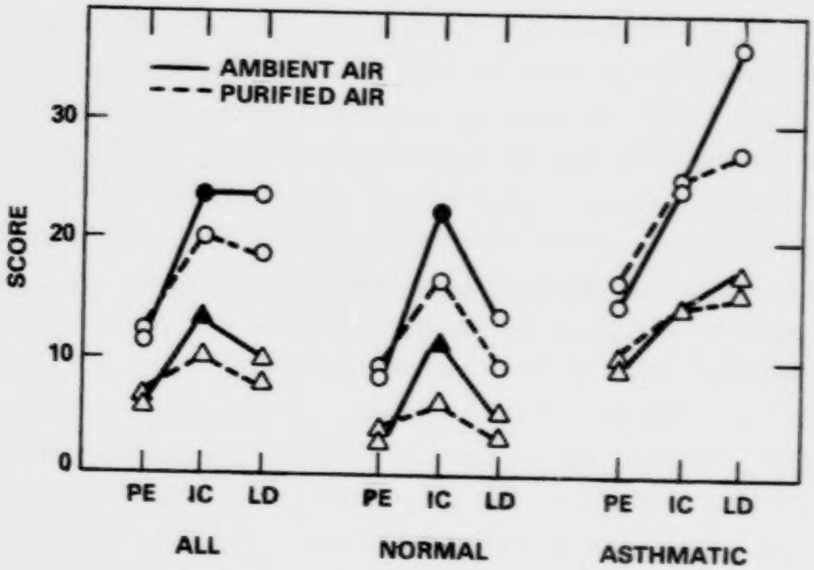

Figure 12-1. Mean symptom score changes with exposure for all subjects, normal and allergic subjects, and asthmatic subgroup of subjects. PE = pre-exposure; IC = in chamber (near end of exposure period); LD = later in day. Circles (○ or ●) indicate total symptom scores; triangles (△ or ▲) indicate lower-respiratory symptom scores. Solid symbols indicate that ambient exposure score is significantly higher for indicated time period and/or increased significantly more relative to pre-exposure value. Open symbols indicate nonsignificant difference between ambient and purified air scores.
Source: Adapted from Linn et al. (1980).

(Hawthorne) with low O_3 levels (0.04 ± 0.02 ppm, 82 ± 39 $\mu g/m^3$) but with elevated levels of other pollutants. They found no meaningful lung-function or symptom changes, and they concluded that O_3 was primarily responsible for the effects seen in the original study.

A third experiment (Linn et al., 1983; Avol et al., 1983) was conducted at the original oxidant-polluted location (Duarte) with 60 subjects, ages 18 to 55, exercising heavily (four to five times resting minute ventilation) and continuously for 1 hr. The mean O_3 concentration was 314 $\mu g/m^3$ (0.16 ppm) in ambient air (measured by the UV method). Total reported symptoms did not differ significantly between exposure and control (purified-air) conditions. For the complete group, small functional decrements in FEV_1 were found (3.3 percent loss, $P < 0.01$), more or less comparable to those in the original study. A number of the subjects showed functional losses during exposure that were still present after a 1-hr recovery period at rest in filtered air. Those in the most reactive quartile (those who experienced 320 to 1120-ml losses, versus control) were compared with the least reactive quartile (increases of 60 to 350 ml). They did not differ by age, height, sex, smoking, medication use, prevalence of atopy, or asthma. Negative FEV_1 changes seemed to occur more frequently (34 of 47 cases) at O_3 exposure concentrations above 235 $\mu g/m^3$ (0.12 ppm), up to 549 $\mu g/m^3$ (0.28 ppm) in the total study group ($P = 0.02$). The authors stated that the considerable functional losses in this study were not necessarily accompanied by symptoms, nor were they related to obvious prior physical or clinical status.

A fourth study in the original location (Duarte) studied 98 subjects, including 50 asthmatics (Linn et al., 1983; Avol et al., 1983). Mean exposure was 306 $\mu g/m^3$ (0.156 ppm) O_3 and 166 $\mu g/m^3$ TSP (lower than in 1980). The highest exposure concentration was 431 $\mu g/m^3$ (0.22 ppm), which was lower than in 1982. The subjects were exposed to heavier, continuous exercise (though lower exercise ventilation levels than in 1980), and those showing the largest changes in pulmonary function (positive and negative) were the asthmatics. The mean decreased values remained depressed for up to 3 hr post ambient exposure. Maximum mean changes in FVC and FEV_1 for asthmatics after ambient exposure were 122 ml and 89 ml, respectively, with the former returning more quickly to control levels. The value for $\dot{V}_{max50\%}$ was more variable with a maximum mean change of 132 L/s after ambient exposure. The only significant mean changes after exposure were for FVC in normals ($P \leq 0.003$). There were significant interactions of ambient and purified air after exposure in asthmatics for FEV_1 and $\dot{V}_{max50\%}$.

In summary, the Linn et al. (1980, 1982, 1983) and Avol et al. (1983) studies have demonstrated respiratory effects in Los Angeles area residents related to O_3 concentration and level of exercise. Such effects include pulmonary function decrements seen at O_3 levels as low as 0.16 ppm and increased symptoms observed at levels as low as 0.12 ppm O_3. The effects are typically mild and generally do not differ substantially between asthmatics and persons with normal respiratory health, although symptoms last for a few hours longer in asthmatics. However, many of the normal subjects had a history of allergy and appeared to be more sensitive to O_3 than "non-allergic" normal subjects. The relative importance of exercise level, duration of exposure, individual variations in sensitivity, and effects of coexisting pollutants in producing the observed effects remains to be more fully investigated.

Lebowitz et al. (1974) demonstrated an association between pulmonary flow and volume changes (measured by a water-filled spirometer) in exercising children under ambient exposure conditions. However, no effects of exercise or diurnal shifts in function during the day were observed under controlled temperature and humidity conditions in filtered rooms; later, Lebowitz et al. (1982b) verified the lack of diurnal effect in normal subjects and validated the use of the Mini-Wright® Peak Flow Meter for field use.

Lippmann et al. (1983) studied 83 nonsmoking, middle-class, healthy children (ages 8 to 13) during a 2-week summer day camp program in Indiana, PA. The children exercised outdoors most of the time. Afternoon measurements included baseline and post-exercise spirometry (water-filled, no noseclips). Peak flow rates were obtained by Mini-Wright® spirometer at the beginning of the day or at lunch, both adjusted for age and height. No day-of-week effect was seen. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler in the day camp building rooftop. Ozone concentrations were estimated as a weighted average of data extrapolated from a monitoring site 20 mi south and a site 60 mi west, using two models that yielded O_3 estimates within ±16 $\mu g/m^3$ (0.008 ppm) on average. Estimated 1-hr peak O_3 levels (early afternoon) varied from 90 to 249 $\mu g/m^3$ (0.046 to 0.122 ppm), whereas TSP levels were low (6-hr samples $\leq 103\ \mu g/m^3$), as were sulfuric acid (H_2SO_4) equivalent concentrations (maximums $\leq 6.3\ \mu g/m^3$). Lippman et al. (1983) reported significant inverse correlations between FVC and FEV_1 and estimated maximum 1-hr O_3 levels for 4 or more days covering a twofold range in O_3. Differences in correlations (i.e., slopes) were not related to other pollutants (TSP, H_2SO_4) or ambient temperatures. Qualitatively, the Lippmann et al. (1983) study results suggest low-level O_3 effects; however, because exposure modeling (rather than on-site monitoring) was used to estimate O_3 levels, much uncertainty surrounds quantitative interpretation of the study results. The uncertainty about appropriate quantitative interpretation of these findings may be reduced by consideration of the results from a similar study conducted the next summer by Lippmann and Lioy (1984).

A similar group of children was studied at a day camp in Mendham, NJ. Preliminary analyses of the Mendham data, as summarized by Lippmann and Lioy (1984), indicates a significant association between peak hour O_3 levels and decrements in peak expiratory flow rate (PEFR). In order to provide better air monitoring data, O_3 concentrations were measured (UV) at the Mendham camp site, as were concentrations of H_2SO_4. The highest peak 1-hr O_3 concentration measured on a study day was 0.143 ppm; values ranged from 0.02 to 0.18 ppm O_3.

Several comparisons can be made between the data reported by Lippmann et al. (1983) and Lippmann and Lioy (1984). There were 39 children (22 girls, 17 boys) in the follow-up study with sufficient data for analysis; however, the children were not as physically active as the children studied in the previous study in Indiana, PA. While marked O_3-dependent changes in PEFR were reported, Lippmann and Lioy (1984) did not observe an O_3-dependent change in FVC, as was found previously. Also, the change in $FEV_{1.0}$ with O_3 was smaller in girls. However, in both studies, the O_3-related decrements were greater in girls than boys. Both studies also reported low concentrations of acidic aerosol, suggesting that the response was primarily attributable to O_3. A final analysis of the two studies cannot be made until a complete description of the results obtained in Mendham, NJ, has been published.

12.2.2 Symptoms and Pulmonary Function Under High-Altitude Conditions

Young et al. (1962) noted high average O_3 levels in passenger cabins of aircraft flying between 27,000 and 39,000 feet. In 1973, Bischof reported that O_3 concentrations (Comhyr ECC meter) during 14 spring polar flights (1967-71) varied from 0.1 to 0.7 ppm, with 1-hr peaks above 1.0 ppm, despite ventilation. More recently, Daubs (1980) reported O_3 concentrations in Boeing 747 aircraft ranging from 0.04 to 0.65 ppm, with short-term (2 to 3 min) levels as high as 1.035 ppm. Other reports (House of Representatives, 1980; Broad, 1979) indicate that O_3 concentrations in high-altitude aircraft can reach excessively high levels; for example, from New York to Tokyo a time-weighted concentration of 0.438 ppm was recorded, with a maximum of 1.689 ppm and a 2-hr exposure of 0.328 ppm.*

Anecdotally, flight attendants and passengers in high-altitude aircraft have complained of certain symptoms (chest pain, substernal pain, cough) which were most prevalent during late winter and early spring flights. Similar symptoms have been observed in more systematic studies of such effects, such as (1) the study by Reed et al. (1980), which found symptoms among 1,330 flight attendants to be related to aircraft type and altitude duration but not to sex, medical history, residence, or years of work; and (2) the Taskin et al. (1983) study, which found increased O_3-related symptoms in flight attendants on Boeing 747SP (higher-altitude) flights in comparison to attendants on lower-flying 747 flights. Neither of these two studies, however, measured O_3 concentrations in the aircraft studied.

Two recent studies by Lategola and associates attempted more quantitative evaluation of problems associated with O_3 exposures of flight attendants and passengers. Lategola et al. (1980a) exposed 55 young subjects (29 men and 26 women) to ambient air and to an O_3 environment in an altitude chamber maintained at 1829 m (6000 ft). Subjects served as their own controls in each experiment. Two major studies were conducted on 27 (15 men and 12 women) and 28 (14 men and 14 women) subjects.

In the first study, (1) O_3 concentrations were 0 and 315 $\mu g/m^3$ (0.0 and 0.2 ppm), (2) exposure time was 4 hr (with four 10-min exercise periods, the first three being at lower levels of activity and the fourth at a higher level) and (3) pulmonary function and subjective evaluations were obtained pre- and post-exposure. These measurements were made near sea level before and 10 min after the altitude exposures. Other studies, on vision parameters, hand steadiness, and Wechsler memory tests, were conducted during the high-altitude exposures. Male subjects exercised with minute ventilations of 20 L/min in the first three exercise periods and 30 L/min for the last period just prior to descent; for female subjects, exercise ventilations were 13 and 17 L/min, respectively. No alterations in the measured pulmonary functions were found and although slight discomforts were reported, they were not significantly related to O_3 exposure. The second study differed from the first in that the O_3 exposure was 475 $\mu g/m^3$ (0.3 ppm) and only three exercise periods were used. Again, men exercised at ventilations of 24.9 L/min for the first two periods and 38.6 L/min for the last, and the women at 16.4 and 20.9 L/min, respectively. Significantly greater symptom scores were found after both the last exercise period and the termination of the study. In this experiment, differences between the no-O_3 and the O_3 responses for all spirometry parameters [FVC, FEV_1, forced expiratory flow ($FEF_{25-75\%}$), and $FEF_{75-95\%}$] within each sex group were statistically significant ($P < 0.05$). The two lung-volume measures manifested smaller changes than did flow-rate flow measures. Symptom scores were greater in men than in women during the last treadmill tests, but were not statistically significant. The results indicate increased symptoms and pulmonary function decrements among normal subjects at 0.30 ppm, but not 0.2 ppm under light exercise conditions.

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*Note that, as ambient pressure decreases at high altitude, O_3 concentrations remain the same as expressed in terms of ppm levels, but O_3 mass concentrations (in $\mu g/m^3$) decrease in direct proportion to increasing altitudes. Therefore, knowledge of prevailing atmosphere pressure and temperature is generally needed for correct conversion of ppm O_3 readings to $\mu g/m^3$ O_3 concentrations under specific measurement conditions.

Lategola et al. (1980b) also studied 40 middle-aged men, 20 smokers and 20 nonsmokers, again exposed in an altitude chamber (1829 m), resting for 3 hr in environments containing 0 or 475 $\mu g/m^3$ (0.0 or 0.3 ppm) O_3. Eye discomfort was the most frequently reported symptom; headache and nose and throat irritation were also reported. All subjects combined manifested small but statistically significant spirometric decrements in FVC, FEV_1, and $FEF_{75-95\%}$, primarily due to changes within the nonsmoking group. Smokers reported fewer or diminished symptoms, confirming observations reported by others. The study tends to confirm small but significant respiratory effects observed at 0.3 ppm among nonsmoking normal adults under high-altitude conditions. The O_3 levels used in the Lategola studies are, however, generally lower than O_3 concentrations reported to occur in certain aircraft at high altitudes, as are the simulated altitudes employed by Lategola and coworkers.

12.3 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF ACUTE EXPOSURE

Effects of acute exposure to photochemical oxidants are generally assessed in communities by comparing functional or clinical status during periods of high and low O_3 or oxidant concentrations. Occasionally, communities with different concentrations are compared. The concentrations measured have been 24-hr averages, maximum hourly averages, or instantaneous peaks.

12.3.1. Acute Exposure Morbidity Effects

For purposes of this document, indices of acute morbidity associated with photochemical oxidants include the incidence of acute respiratory illnesses; symptom aggravation in patients with asthma and other chronic lung diseases; eye irritation; headache; respiratory irritation; and effects on pulmonary function, athletic performance, auto accident rates, school absenteeism, and hospital admissions.

12.3.1.1. Respiratory and Other Symptoms of Irritation. Various symptoms, including eye irritation, have been reported during ambient air exposure. However, eye irritation has generally not been associated with O_3 exposure in controlled laboratory studies (Chapter 11). This symptom has been associated with formaldehyde, acrolein, and other organic photochemical reaction products such as peroxyacetyl nitrate (PAN) (National Air Pollution Control Association, 1970; Altshuller, 1977; Environmental Protection Agency, 1978; National Research Council, 1977; Okawada et al., 1979). Of the biological effects caused by or aggravated by photochemical air pollution, eye irritation appears to have one of the lowest thresholds; however, it also appears to be a short-term, reversible effect, since damage to conjunctiva and subjacent tissue has not been reported.

Regression analyses by Renzetti and Gobran (1957), as reviewed previously (Environmental Protection Agency, 1978), has indicated increases in eye irritation over a wide range of average oxidant values in the Los Angeles area, suggesting that severity increased above hourly oxidant concentrations of about 0.1 ppm.

The U.S. Environmental Protection Agency (1978) also reviewed several studies on 850 Japanese schoolchildren by Shimizu (1975) and Shimizu et al. (1976), by the Japanese Environmental Agency (1976), and by Makino and Mizoguchi (1975) and Mizoguchi et al. (1977). The Shimizu et al. studies did not segregate the effects of oxidants, although they found that acrolein (0.5 ppm, 5 min) produced eye irritation. The Japanese Environmental Agency (1976) study reported complaints from a survey conducted at oxidant concentrations >0.15 ppm, but without denominators. In the studies by Makino and Mizoguchi (1975) and Mizoguchi et al. (1977), no yearly symptom-pollution correlations were significant for SO_2, NO_2, or NO alone, whereas some symptoms were positively correlated with temperature (alone and with other pollutants). The highest correlations were reported between symptoms and oxidants. On days when maximum hourly oxidant levels exceeded 0.10 ppm, significantly higher rates of eye irritation, cough, headache, and sore throat were reported. Analyses of further studies, which measured oxidants (KI) and O_3 (chemiluminescence) on a schoolground, yielded similar results. When maximum oxidant concentrations exceeded 0.15 ppm, eye irritation, sore throat, headache, and coughing were greater than on lower-oxidant-level days. Infectious illnesses were not distinguished. Symptom rates in 74 allergic students were generally higher than rates in nonallergic or all students on days when the maximum hourly oxidant level was 0.23 ppm or greater. These and other subjective symptoms were reported during episodes of acute smog in Japan, although rates (i.e., denominators) were unknown, and other pollutants were present at high concentrations (Kagawa, 1982; Kabayama, 1971; Fujii, 1972; Mikami and Kudo, 1973a,b; Adachi et al., 1973; Adachi and Nakajima, 1974; Matsumura et al., 1973; Sugita et al., 1976; Masuda, 1977). Weather variables were not controlled in the analyses of data from these studies. Effects seen at different times of the day during episodes in Japan may be due to different pollutant mixes.

In the more recent literature, Okawada et al. (1979) examined the associations between eye irritation and photochemical oxidants in Tokyo high school students 7 days during two summer sessions (n = 28 and 43, respectively). Tests were performed between 1:00 and 4:00 p.m., during periods of daily maximum oxidant levels (measured by KI method at test site). Tear lysozyme and pH values were measured, and eyes were examined with a slit-lamp. Tear lysozyme and pH values decreased on 2 days when the oxidant concentration was highest (0.175 and 0.210 ppm), in comparison to 2 days when the concentration was lowest (0.020 to 0.033 ppm). Eye irritation incidence rates (determined from questionnaire responses each day) increased proportionately with oxidant concentrations above 0.1 ppm. The irritation was produced experimentally with the following pollutants individually: formaldehyde ≥ 0.2 ppm, PAN > 0.05 ppm, and peroxybenzoyl nitrate (PBZN) > 0.01 ppm.

Several studies have also reported respiratory and other symptoms associated with photochemical oxidant pollution. One such U.S. study was performed by Hammer et al. (1974) on similar groups of freshman student nurses at two hospitals in Los Angeles, as previously reviewed (Environmental Protection Agency, 1978). Symptom rates from daily diaries (a daily average of 61 students) were obtained from October 1961 through June 1964. Simultaneous daily measurements of oxidants (KI method) and other pollutants and maximum daily temperature were available on more than 90 percent of the days in the study from Los Angeles Air Pollution Control District monitoring stations located 1.5 to 3.0 km from both hospitals. Both before and after adjusting the rates by excluding days on which subjects reported fevers (to minimize effects of infections), Hammer and coworkers found eye discomfort at oxidant levels between 294 and 372 $\mu g/m^3$ (0.15 and 0.19 ppm), cough at 588 to 764 $\mu g/m^3$ (0.30 to 0.39 ppm), and chest discomfort at 490 to 568 $\mu g/m^3$ (0.25 to 0.29 ppm) maximum hourly oxidant levels. These adjusted rates were related to oxidant levels more closely than to CO, NO_2, or daily temperature. The rates are shown in Figure 12-2.

Symptoms of cough, chest discomfort, and headache have been both (1) associated with occupational exposure to oxidants (see below) and (2) in some community studies cited above appear to have resulted from exposure to ambient-air oxidants. Some of these effects may have resulted from interactions between oxidants and other pollutants (National Research Council, 1977). Various oxidants may produce irritation at levels found in smog (Dimitriades, 1976; U.S. Environmental Protection Agency, 1978; National Research Council, 1977).

12.3.1.2 Altered Performance. To determine the possible effects of photochemical oxidant pollution on athletic performance, Wayne et al. (1967) and Herman (1972) studied a group of cross-country track runners during meets in Los Angeles. Their results indicated that NO_x, CO, and particulate matter were not related to performance. They did not examine SO_2. The proportion of runners failing to improve their times during the track season significantly rose as concentrations of oxidants measured by the Air Pollution Control District increased to the range of 0.06 to 0.37 ppm in the hour before the race. Subsequent analysis of this study has yielded estimates of impaired athletic performance above 0.12 ppm oxidant (Hasselblad et al., 1976; U.S. Environmental Protection Agency, 1978; World Health Organization, 1978) or 0.065 ppm (National Research Council, 1977). Analysis of an extended set of

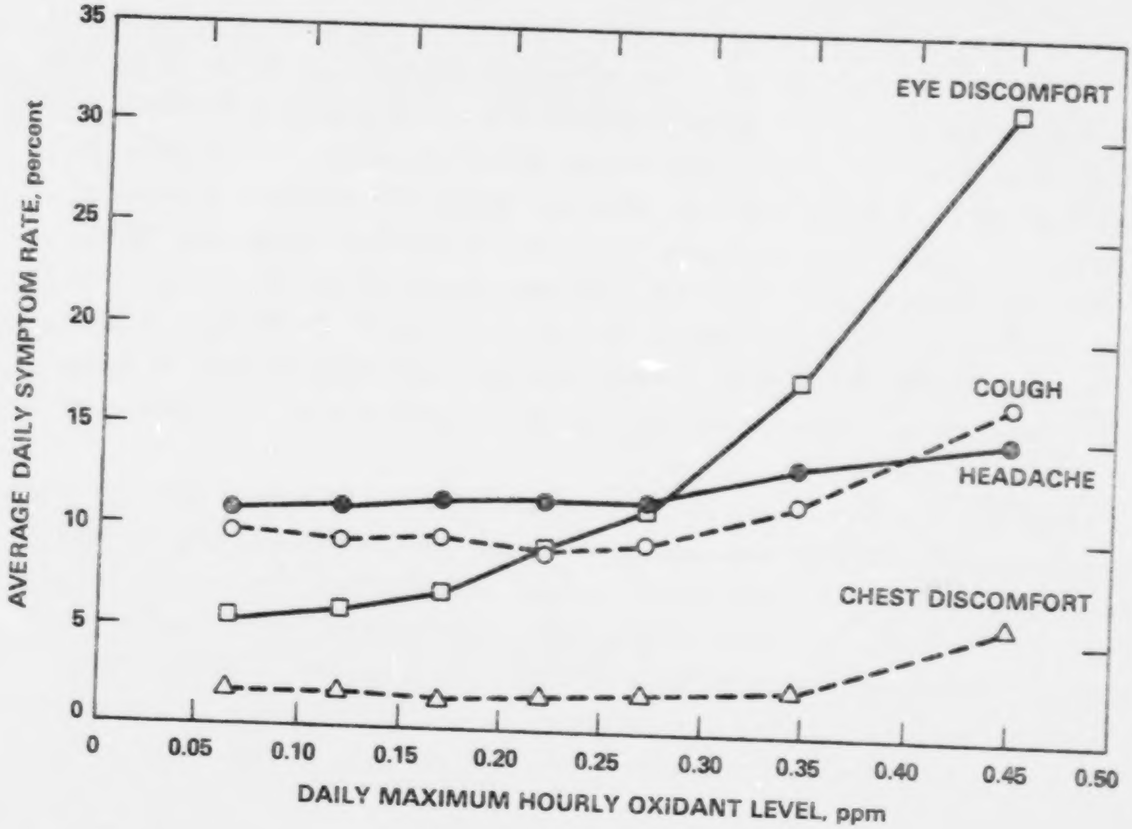

Figure 12-2. Relationship of average daily percent adjusted (i.e., without fever, chill, or temperature) symptoms to photochemical oxidant level, May 1961 - May 1964 (868 days).
Source: Adapted from Hammer et al. (1974).

data by Herman (1972) showed an inverse association between running speed and oxidant measured 1 hr before the meet, after correcting for average speeds, time, season, and temperature.

Some investigators have hypothesized that photochemical oxidant pollution may create poor daytime driving conditions. Ury (1968) found that concentrations of oxidants monitored by the Air Pollution Control Districts correlated positively with the frequency of weekday daylight motor vehicle accidents in Los Angeles during August through October. Accident rates were higher on days when hourly oxidant levels exceeded 0.15 ppm than on days below 0.10 ppm. Other pollutants were not evaluated, but are low in summer. As for weather, only days of rain and fog were excluded from data analyses. In a second study, Ury et al. (1972) investigated CO concentrations during winter months with the same analytical methods. A statistically significant difference in frequency of accidents above and below 0.10 ppm was again noted in relation to oxidant concentrations, but no consistent relationship was noted with lagged oxidant or CO concentrations. Morning (9:00 a.m. to 12:00 noon) peaks in accidents may implicate O_3 precursors or other pollutants, but do not implicate traffic density. Reduced visual acuity (according to results of Lagerwerff, 1963), increased eye irritation, or reduced visibility may have been partly responsible (U.S. Environmental Protection Agency, 1978).

12.3.1.3 Acute Effects on Pulmonary Function. Previously reviewed studies (U.S. Environmental Protection Agency, 1978) showed significant differences in children's peak flow rates related to oxidants in two Los Angeles communities (McMillan et al., 1969) but no differences in pulmonary function in office workers in Los Angeles and San Francisco (Linn et al., 1976). Neither study measured pollutant exposures sufficiently or accounted for meteorological variables; also, within-study populations appeared to differ between communities.

Kagawa and Toyoma (1975) and Kagawa et al. (1976) reported consistent effects of O_3 on the pulmonary function of children in Japan. First, they studied 21 children 11 years of age (in 1975) for 29 weeks (June-December). Hourly average concentrations of O_3 (measured by chemiluminescence) at their school ranged from 20 to 294 $\mu g/m^3$ (0.01 to 0.15 ppm). Maximum hourly concentrations of NO, NO_2, and SO_2 were approximately 98 $\mu g/m^3$ (0.08 ppm), 432 $\mu g/m^3$ (0.23 ppm), and 133 $\mu g/m^3$ (0.05 ppm), respectively, and particulate matter was 350 $\mu g/m^3$. The overall significance of the association between O_3 and pulmonary function tests was accounted for by 25 percent of the subjects, in whom airway resistance (R_{aw}) was positively correlated with O_3 concentrations during testing, specific conductance (SG_{aw}) was negatively correlated, and maximum expiratory flow rates ($\dot{V}_{max50\%}$, $\dot{V}_{max25\%}$) were inconsistent. These measures also correlated with temperature (more than with any other variable) and SO_2 levels, but not with NO_2 levels.

The same students were studied during a low-temperature period (November-March) and a high-temperature period (April-October). Hourly average O_3 concentrations ranged from about 20 to 588 μg/m^3 (0.01 to 0.30 ppm); NO, NO_2, and SO_2 concentrations were approximately 220, 563, and 418 μg/m^3 (0.18, 0.30, and 0.16 ppm) respectively, and the concentration of particulate matter was approximately 450 μg/m^3. Again, concentrations of O_3 were positively correlated with R_{aw}, $\dot{V}_{max50\%}$, and $\dot{V}_{max25\%}$ and negatively correlated with SG_{aw}, in both periods, and more consistently in the low-temperature period when O_3 was lowest (<0.10 ppm, 196 μg/m^3). As in the previous study, associations of function with pollutants were confounded by temperature, which acted differently in the two seasons. Excluding the effect of temperature yielded several O_3-R_{aw} and O_3-$\dot{V}_{max50\%}$ partial correlations of statistical significance in the low-temperature (low-O_3) period. Analysis of multiple correlation coefficients indicated a few likely pollutant interactions. R_{aw} and SG_{aw} correlated with multiple environmental variables in nine subjects. There were linear relations of health effects with O_3 concentrations occurring up to the maximum concentrations: 0.15 ppm in the first study, (high-O_3 period) and either 0.10 (as the effects were seen in the low-O_3 period) or 0.30 ppm (in the high-O_3 period) in the second study. Another Japanese study (Shishido et al., 1974) showed similar results, but did not control for other pollutants.

Lebowitz et al. (1982a, 1983) and Lebowitz (1984) studied 24 children and young adults, ages 8 to 25, from middle-class backgrounds for an 11-month period in 1979 and 1980 in Tucson, AZ. Every day, in the late afternoon (3:00 to 7:00 p.m., usually 4:00 to 6:00 p.m.) peak flow was measured with a Mini-Wright® peak flow meter (Wright, 1978; Williams, 1979; van As, 1982; Lebowitz et al., 1982b). Subsets of the group, chosen randomly, underwent measurements during different seasons of the year. After age and height correction, no peak flow differences in baseline data were seen among the subjects by analysis of variance (ANOVA), and all were within the published normal range (within 1 standard deviation of 100 percent of prediction). Daily peak flows for each child were transformed into a standard normal variable ($\bar{x} = 0$, $s = 1$), using the formula $z_i = (x_i - \bar{x})/s$. The seasonal mean and standard deviation were used to generate daily values (z-scores) that were standardized deviations from seasonal averages, with similar units for all individuals. This procedure adjusts for seasonal effects and differences between individual means and variances.

Ozone (measured by chemiluminescence), CO (infrared), and NO_2 (chemiluminescence) were monitored outdoors at three stations. Daily TSP level (6-day high-volume samples) was measured at 12 locations, including stations at the center of each cluster of subjects within a 1/4- to 1/2-mi radius). Previous inventories by the Pima County Air Quality Control District (1978) showed significant homogeneity of O_3 in the basin. The central station data and the average basin data were used in the analysis. Comparisons of these data showed no significant differences in results between the two. In this study, indoor O_3 (chemiluminescent method) showed very low levels (<0.035 ppm, 69 $\mu g/m^3$) as reported previously (National Research Council, 1981). Indoor and outdoor CO levels were less than 2.4 ppm (2736 g/m^3) and 3.8 to 4.9 ppm (4332 to 5586 g/m^3), respectively, as was NO_2 (median of 0.03 ppm, 34 $\mu g/m^3$). Indoor CO was correlated with gas-stove use only. Outdoor TSP ranged between 20 and 363 $\mu g/m^3$ for all monitoring days and between 27.5 and 129 $\mu g/m^3$ on days of indoor monitoring. Indoor TSP and respirable suspended particle (RSP) ranges for 41 representative houses were 5.7 to 68.5 $\mu g/m^3$ and 0.1 to 49.7 $\mu g/m^3$, respectively, and were correlated with indoor cigarette smoking but not gas-stove use (Lebowitz et al., 1983; Lebowitz, 1984).

Initial analysis showed that O_3 and TSP levels were negatively correlated with peak flow, after correcting for season and other pollutants. Multivariate analysis of variance was conducted to control for person days of observation, meteorological variables, CO, NO_2, and TSP, after which the O_3 concentration coefficient was still shown to be independently significant ($P < 0.001$). There were significant, independent interactions between O_3 and TSP with peak flow (see Table 12-3).

When the contributions from each of the other factors were removed by adjustment (using multiple regression), the O_3 concentration correlation with peak flow was still significantly negative (Lebowitz et al., 1983). The mean z-score for the person days with a maximum hourly O_3 level of 157 $\mu g/m^3$ (0.08 ppm) or greater (21 days) was -0.31 ($P < 0.007$); it was -0.38 for a mean O_3 level of 157 $\mu g/m^3$ (0.08 ppm) or greater between 3:00 and 7:00 p.m.

TABLE 12-3. THE RELATIONSHIP BETWEEN AVERAGE STANDARDIZED DEVIATIONS OF PEAK FLOW AND OUTDOOR CONCENTRATIONS OF OZONE AND TOTAL SUSPENDED PARTICULATE MATTER[a]

Maximum hourly ozone concentration		Daily total suspended particulate matter,[b] (μg/m³)			
μg/m³	ppm	<56	56-76	≥77	All[c]
<75	<0.038	+0.108 (167)[d]	+0.239 (53)	+0.156 (61)	0.069 (663)
75-100	0.038-0.051	+0.042 (71)	-0.162 (39)	-0.061 (39)	0.024 (363)
102-155	0.052-0.079	+0.242 (40)	-0.021 (94)	-0.474 (67)	-0.115 (419)
157-235	0.08-0.12	-0.088 (9)	-0.196 (31)	-0.804 (27)	-0.310 (148)
All		0.115 (298)	-0.027 (244)	-0.227 (223)	

Source: Lebowitz (1983a).

[a] Analysis of variance for total explained effect, for the interaction, and for each pollutant, $P < 0.0001$.

[b] Sample size was reduced because total suspended particulate matter (TSP) levels were not available for all days.

[c] Represents all days when data were available for each pollutant.

[d] Person days of observation.

Note: Peak flow decreases with increasing TSP, becoming statistically significant only at ozone ≥ 0.052 ppm. Peak flow also decreases with increasing ozone, becoming significant at TSP ≥ 77 μg/m³ (the decrements at ozone ≥ 0.08 ppm are significant for TSP levels of 57-76 μg/m³). There is a very significant interaction of ozone and TSP. Decrements in peak flow of -0.474, -0.804, and -0.310 represent 18, 28, and 12% changes respectively, when compared to normal day-to-day variability in a comparable group of children previously studied by Lebowitz et al. (1982b).

($P < 0.0001$). The z-scores represent decreases in peak flows of 12.2 percent and 14.8 percent, respectively, and the percent changes are significant ($P < 0.05$), based on published data for normal day-to-day variability in another, comparable group of children (Lebowitz et al., 1982b). This study, because of the small number of subjects, needs to be repeated to determine the consistency of the relationships found. Personal monitors, had they been available, would have provided more accurate exposure estimates. Children are likely to spend much time outdoors, especially in the afternoon.

12.3.1.4 Aggravation of Existing Respiratory Diseases. Several studies have examined photooxidant pollutant effects on symptoms and lung functions of patients with asthma, chronic bronchitis, or emphysema. Most earlier ones were evaluated in the predecessor criteria document (U.S. Environmental Protection Agency, 1978). Schoettlin and Landau (1961) reported increased daily asthma attacks in 137 subjects from September to December, 1956, on high oxidant days in Los Angeles, but did not control for age, sex, temperature, season, or medication use. Schottlin (1962), using regression analyses, found no relationship between oxidants (KI) and symptoms in 200 chronic lung disease patients and 200 matched controls from a Los Angeles Veterans Administration hospital. Rokaw and Massey (1962) performed a pilot study on 31 chronic pulmonary patients and a control group in Los Angeles over an 18-month period, using pulmonary function tests four times per week. Only six patients showed negative changes associated with higher oxidant concentrations ($\bar{X}$ = 0.06 ppm, max. = 0.42 ppm).

Zagraniski et al. (1979) studied a group of 82 asthmatic and allergic (i.e., hay fever) patients and a group of 192 normal telephone company employees in New Haven, CT, from July to September 1976. Of the two groups studied, 57 percent were female, 90 percent white, 61 percent over age 30, 35 percent current smokers (20 percent more than one pack per day), and 22 percent ex-smokers. The clinic group (i.e., asthma and allergic patients) had higher proportions of ex-smokers and persons who had never smoked, whereas the employee group had significantly more women, persons over 30, and persons who held clerical or technical jobs. All these variables were controlled in statistical analyses of data from daily diaries (completed weekly over a 10-week study period).

Air monitoring occurred at two sites 1.2 km apart and within 0.8 km of where the subjects were recruited; however, distances from residences and workplaces were not reported. Concentrations of SO_2, TSP, sulfates (from dried glass-fiber filters), and O_3 (by chemiluminescence) were monitored; previous monitoring had shown low NO_2 and CO levels. Meteorological variables, specifically maximum daily temperature (mean of 27°C, from 19 to 34°C), were used as covariables. Average daily windspeed varied little and was not used. Sulfates and O_3 often had coincident peaks; few daily sulfate concentrations exceeded 24 $\mu g/m^3$. Ozone maximum hourly readings averaged 157 $\mu g/m^3$ (0.08 ppm), and the range was 8 to 461 $\mu g/m^3$ (0.004 to 0.235 ppm), with maximum concentrations in the afternoon. Eight-hour mean TSP was 83 μg/m^3 (range: 24 to 169 μg/m^3), and 24-hr mean TSP was 73 μg/m^3 (range: 20 to 147 μg/m^3). Reported outdoor exposure, working, and home conditions were judged to be equivalent for most subjects for most pollutants.

Daily symptom prevalence rates were used as dependent variables. Patients had higher symptom rates, except for cough, than did controls. Smokers in both groups reported more episodes of illness and chronic productive cough than did nonsmokers. Data from participants who returned five or fewer daily records per week or missed four or more consecutive weeks of the study were excluded from analysis, and 23 percent of the participants (10 percent controls; 50 percent patients) dropped out of the study. The dropout rate was related to smoking in both groups and to asthma and allergy exacerbations in the patients. Symptoms rarely correlated with pollution variables, using paired and multiple analyses. Maximum hourly O_3 levels correlated with cough and nose irritation in heavy smokers ($r = 0.24$ and 0.32, respectively, $P < 0.05$), and significant positive, pairwise correlations ($P < 0.05$) of maximum hourly O_3 levels were found with cough in hay fever patients ($r = 0.22$), and with nose irritation in asthmatics ($r = 0.17$). When subjects were regrouped by smoking and illness status for multiple regression analyses, O_3 level significantly (independently) correlated with cough and eye irritation in heavy smokers, and with cough in hay fever patients (independent of season). Cough frequency increased linearly with hourly O_3 concentrations in the range of 8 to 461 μg/m^3 (0.004 to 0.235 ppm, a mean of 0.08 ppm), especially in smokers and in those with predisposing illnesses (independent of season). No other symptoms were associated with O_3 in any of the groups, nor were other pollutants associated with symptoms. Negative pH changes of TSP over 8 hr and 24 hr were positively and independently associated with eye, nose, and throat irritation in most groups, but not with other symptoms. Pollen was associated positively only with frequent sneezing in hay fever patients.

A major problem with this study is that daily prevalence data were used, rather than incidence data, and no correction for auto regression was made (see below). Misinterpretation and misuse of diaries were limited in frequency, as determined from comparisons with clinical data, and were not likely to have substantially influenced symptom data. However, bias may have been induced (in either direction) by the selective dropout of the more heavy smokers, the patients with symptoms, and persons who did not report symptoms. These factors should have been evaluated.

Whittemore and Korn (1980) reported newly developed statistical methods by which they evaluated daily asthmatic attack rates recorded in diaries by asthmatics residing in the Los Angeles area for 34-week periods (May to December) during 1972 to 1975. The panels were recruited by the U.S. Environmental Protection Agency (EPA) as part of the Community Health Environmental Surveillance System (CHESS), and participants were asked to complete weekly diaries. Diaries not received within 16 days after each week were discarded. (The EPA data sets used have undergone quality control to ensure accurate coding of health responses.) The 16 location-specific panels were chosen by local consulting physicians, differed from one another in size and composition, and were not expected to be representative of the asthmatic population. Information on demographic variables, smoking, occupational exposures, and other factors potentially related to asthmatic attacks indicated great interpersonal variability. Air pollution measurement (24 hr; midday to midday) periods were derived from EPA monitors in each of the six communities for all pollutants except oxidants. Daily maximum hourly averages for oxidants (KI) were used, as measured by the County Air Pollution Control Districts. Each individual in each 34-week period was considered separately in multiple logistic analyses (without respect to place). Many individuals were therefore counted in more than one 34-week period. There were 444 such person periods (166 males under 17, and 65 males over 17; 94 females under 17, and 119 females over 17). Homes were within 1 to 8 mi (average of 3 mi) from the monitoring sites. Since RSP, NO_x, and SO_x were highly correlated with TSP, TSP was chosen as an index for the mix of other pollutants. Weather variables, i.e., temperature, relative humidity (rh), and average wind speed, were included in the regressions, as were day-of-week indicators.

Daily oxidant levels ranged from 0.03 to 0.15 ppm between areas and between times. Each daily attack rate was regressed by multiple logistic regression function against the presence or absence of attacks on the preceding day (to correct for an autocorrelation effect), the daily representative levels of oxidant and TSP, minimum temperature, rh, and average windspeed, as well as against variables representing time since the start of the study and day of week. Days with missing attack data, as well as days with missing pollutant data, were not included in the regressions. The autocorrelations of asthma were the most significant variables in the logistic regressions. The other air pollution and weather variables were also independently significant, except for windspeed (which was later dropped). Baseline probabilities of attacks were determined, dependent upon whether or not an attack had occurred on the previous day. Relative risk probabilities for attacks being associated with specified increases in oxidant levels were also estimated by the model, holding all other variables constant. Counts of expected (from the model) and observed attacks (from the Los Angeles diary data) were then compared to determine how well the model predicted actual data. Although the panel coefficients obtained for oxidant and TSP indicate a number of consistent effects (not all panels show such effects), intrapanel variability with respect to temperature and humidity suggests high individual variability in responses. Also, days of cool temperature elicited significantly high attack rates. The relative importance of day of week, day of study, and attack on preceding day indicate that panel studies should include these factors in the study design. Results obtained indicated, for example, that panelists having a baseline attack probability of 0.10 following an attack-free day and an attack probability of 0.41 on the day after an attack day, would have the attack probability on a given day raised to 0.13 or 0.44, respectively, if oxidant levels increased by 0.2 ppm. Similarly, even smaller increments ($\leq$0.01) in relative risk for attacks were estimated to be associated with increases of 0.10 ppm in oxidant levels. No consistent departures from the model were noted in examining deviations of observed from expected values, indicating that the actual data fit the model quite well. However, caution is demanded before fully accepting the obtained quantitative findings. Use of daily averages of pollutant concentrations from monitors distant from the subjects may not have been sufficient or appropriate, and the analyses did not use data on medication use, pollen counts, daily emotional stress, other pollutants, exercise (e.g., in cool weather), or respiratory infections (because these data were not collected). The effects of such omissions could not be tested. Also, the ascertainment of attack was based on subjective appraisal, without clinical validation, leading to possible biases in reporting. Last, some data on attacks were missing, and, as with most epidemiological studies, information on actual subject exposure can only be inferred. Shy and Mueller (1980), commenting on the study, further indicated that a repeated measure design using analyses of variance would have allowed an evaluation of the interaction of group and time, with fewer comparisons necessary, and reduced cases where an individual occurs in more than one panel.

In another study of exacerbation of preexisting respiratory disease, Lebowitz et al. (1982a, 1983) and Lebowitz (1984) studied 117 families (229 subjects) from a stratified sample of families in three geographic clusters in a community study population. Families were chosen to be representative of the Anglo-white population, stratified by symptoms, and monitored over a 2-year period, using daily symptom and medication diaries and mini-Wright® peak flow meters (Wright, 1978; Williams, 1979; Lebowitz et al. 1982b; van As, 1982). Daily response rates were acceptable for a majority of days in all seasons. Checks by telephone and visits ensured proper use of diaries, and visits were made to calibrate peak flow meters. All families provided information on their houses, heating, cooling, and appliances, and smoking in the household.

Twenty three adult asthmatics in one cluster, and a total of 35 adult asthmatics, provided daily peak flows. There were 353 days with sufficient information (>5 individuals/day) for analysis. There were additional days with sufficient information ($n > 5$) on separate subgroups: 544 days from adults with reported chronic symptoms of airway obstructive diseases (AOD), 494 days from adults with reported allergies, and 312 days from asymptomatic adults. For adults, z-score transformation (see above) of peak flows used sex-, age-, and height specific values. Thus, all peak flows ($\dot{V}_{max}$) were adjusted for covariables and were in the same relative units. When the individual was the unit of study, a person-days dummy variable was used in analysis to eliminate effects of the different number of individual person days of observation. Multivariate analyses of variance and regression methods were used to examine interactions and to control for colinear variables.

Indoor and outdoor (around the residence) monitoring was conducted in a random cluster sample of study households ($n = 41$) for air pollutants, pollen bacilli, fungi, and algae. Monitoring for pollen and TSP (measured by the high-volume method) was conducted simultaneously in the center of each cluster, and pollutants were measured regionally in the basin (see previous discussion for details). Symptom rates per 100 person days were calculated from daily diary data for asthmatics and nonasthmatics within exposure groups for comparative purposes. Attempts to estimate concentrations in houses not monitored yielded a classification based on gas-stove use and smoking in the houses. Scanning electron microscopy showed that indoor dust differed from outdoor dust, which was generally almost all silica quartz (mass median aerodynamic diameter, MMAD, of ~ 5 μm), and rapid fall-off was observed for outdoor particles and pollen as participants entered their houses (decreasing 100 to 200-fold).

For adults, smoking had the biggest effect on $\dot{V}_{max}$. In adults with AOD symptoms, O_3 was significantly related to $\dot{V}_{max}$ ($P < 0.01$) after adjustment was made for smoking and relative humidity as covariables, and TSP and gas-stove use as other main effects. Concentrations of TSP were also significant ($P < 0.01$), and the O_3-TSP interaction had a P of 0.104 (n = 258 days). Using the same variables in multiple regression yielded a regression coefficient of -5.946 for O_3 ($P < 0.005$ by t-test) and a regression coefficient of + 0.004 ($P < 0.0025$) for TSP.

In 23 asthmatics in one geographic cluster where indoor monitoring was most complete, O_3 and temperature had a significant interaction in relation to $\dot{V}_{max}$; high temperature had an effect when O_3 was low, and O_3 had an association with $\dot{V}_{max}$ only in low temperatures (Table 12-4). However, O_3 was not independently related to $\dot{V}_{max}$ after adjustment was made for outside CO, temperature, humidity, age, smoking, gas-stove use, indoor TSP, and residential pollen (fungi were not independently important). There was also an interaction of O_3 and temperature with prevalence rates of acute symptoms in these asthmatics. Temperature was more important, since O_3 had an effect (though not statistically significant) only within the high-temperature range. (Since only 75 incidence days of asthma attacks occurred in 3820 person days, incidence rates could not be evaluated.) Ozone was associated with prevalence of rhinitis, but only in those living in houses using gas stoves ($P < 0.015$) in this group, with multivariate analysis of variance controlling for temperature. Daily medication was correlated highly with exacerbations of symptoms.

The O_3 level at which $\dot{V}_{max}$ effects were seen, although consistent, is lower than expected. After controlling for other variables, the authors speculated that the effects in asthmatics were occurring primarily at O_3 concentrations ≥ 0.052 ppm, with O_3 acting either as a surrogate for other oxidants or in conjunction with other environmental conditions (i.e., low temperature, high TSP).

A study of health-related responses to air pollution in persons with chronic obstructive pulmonary disease was conducted in Houston, TX, by Johnson et al. (1979). Javitz et al. (1983) recently presented the results of a reanalysis of this study. Logistic regression of a selected set of self-reported health symptoms from oxidant exposure revealed that the incidence of

TABLE 12-4. THE RELATIONSHIP BETWEEN AVERAGE STANDARDIZED DEVIATIONS OF PEAK FLOW IN ASTHMATICS AND THE INTERACTION OF OZONE AND TEMPERATURE[a]

Maximum hourly ozone concentration		Temperature (°F)		
μg/m³	ppm	<61	61-80	80-96
<75	<0.038	-1.94 (217)[b]	-1.85 (219)	-2.17 (174)
75-100	0.038 to 0.051	-1.99 (327)	-1.78 (490)	-1.75 (388)
≤102	0.052 to 0.122	-2.11 (30)	-1.71 (549)	-1.57 (794)

Source: Lebowitz et al. (1983b).

[a] Analysis of variance for total explained variation and interaction, $P < 0.0001$.

[b] Person days of observation.

chest discomfort, eye irritation, and "feeling worse than usual" increased by 10.1, 7.5, and 2.9 percent, respectively, as PAN concentrations increased from 0 to 0.012 ppm. Incidence of nasal symptoms and respiratory symptoms and use of medication for respiratory symptoms increased by 6.0, 3.4, and 5.2 percent, respectively, as O_3 increased from 0 to 412 $\mu g/m^3$ (0.0 to 0.21 ppm). No increased incidence of any specific nasal or respiratory symptom or of moderate or severe nasal or respiratory symptoms were noted. Linear regressions of spirometry measurements on daily peak O_3 revealed that average FEV_1 decreased by 1.6 percent and FVC decreased by 2.8 percent as O_3 increased from 0 to 412 $\mu g/m^3$ (0.0 to 0.21 ppm). The FEV_1 and FVC changes with total oxidants (O_3 and PAN) were similar to those found for O_3 alone, but were larger in magnitude (FVC and FEV_1 decreased 4.3 percent and 3.2 percent, respectively). Considering the relatively small sample sizes and test to test variability of 5 percent, the magnitude of the effect is small and of questionable significance.

A major shortcoming of this study was that O_3 measurements were missing for about 40 percent of the study's 1026 site days; also, NO_x, hydrocarbon (HC), CO, sulfur oxides (SO_x), particulate matter, PAN, and aeroallergens were measured only at some of the sites. Daily maximum hourly concentrations of O_3 were measured at the monitoring station nearest each subject's residence. However, in two zones, O_3 measurements were substituted from the next nearest zone and the average reading of six continuous O_3 monitors was substituted in a third zone. Thus, the number of O_3 measurements appears insufficient for appropriate exposure information. Personal exposure information was thought to be the weakest link in the analyses (Javitz et al., 1983). Other difficulties arise from the study's design: (1) sample size (286) was not large enough to allow for sufficient subclassification (Javitz et al., 1983); (2) over one-third of the subjects (total grouped/ indexed) reported respiratory symptoms on 100 or more of this study's 114 days, and over two-thirds reported nasal symptoms on 10 or fewer days. This apparent extreme skewing of symptom behavior may have made such information relatively insensitive to any detected pollution effect. Also, Finally, the number (114) of monitoring days may have been insufficient to allow enough variation in exposure variables or effect variables for relationships between the two to be discerned. A low correlation between spirometry and questionnaire variables may indicate low validity of one or the other (Helsing et al., 1979), and the possibility of a differential attack rate based on lags was not studied. Finally, a number of variables (e.g., age, sex, socioeconomic status, migrant pattern, smoking, occupation) may have been interacting in a colinear or confounding fashion, but were not sufficiently assessed in the analyses.

In regression analyses of questionnaire variables, the health endpoint was a proportion of subjects reporting symptoms at each site rather than the presence or absence of symptoms in individual subjects. These analyses were usually pooled across all sites, although sometimes they were pooled across only three sites. Site-specific regression of questionnaire variables does not appear to have been performed. Only in regression analysis of the spirometric variables did the individual serve as his or her own control. Half the spirometric regression analyses appear to have been limited to only one site. Therefore, the type of health endpoints and the methods of analyses are incomplete and inappropriate. Furthermore, insufficient information was available on daily pulmonary function with which to correlate or perform regression analyses against daily pollutant measurements.

12.3.1.5 Incidence of Acute Respiratory Illness. Table 12-5 describes studies relating oxidant levels with the incidence of acute respiratory illnesses. These studies, however, did not meet the criteria necessary for developing quantitative exposure-response relationships.

12.3.1.6 Physician, Emergency Room, and Hospital Visits. Previously reviewed studies (Environmental Protection Agency, 1978) have indicated that oxidant

TABLE 12-5. STUDIES OF ACUTE RESPIRATORY ILLNESS

Reference	Subject matter	Findings
Nagata et al. (1979)	Health insurance records from two locations in Japan, July-September 1975.	No relationships between oxidant levels (average hourly max = 0.066 ± 0.041 ppm) and new acute respiratory diseases. Other pollutants were not studied.
Durham (1974)	Health service visits for respiratory illness in students at five Los Angeles and two San Francisco colleges.	Pharyngitis, bronchitis, and colds associated with oxidant levels on same day and on 7 preceding days. Stronger associations in Los Angeles than in San Francisco. Oxides were measured about 5 mi away. Other pollutants and climatic variables were not controlled.
Pearlman et al. (1971)	Incidence and duration of influenza-like illness, December 1968-March 1969, among elementary school children in five southern California communities.	No relationship between photochemical oxidant gradient and illness rates during an influenza epidemic occurring in a low-oxidant period; all the communities had similar levels.
Wayne and Wehrle (1969)	Absenteeism in two elementary schools, 1962-1963.	No consistent association between oxidant level and absenteeism. Other pollutants were not considered.
Cassell et al. (1969) and Mountain et al. (1968)	Frequency of cough, sore throat, colds, eye irritation, and headaches in a New York City population near the monitoring station.	In summer, symptoms in children <8 years old were related to carbon monoxide (surrogate of ozone and particulate matter). In adult heavy smokers, eye irritation and headache were related to carbon monoxide. Maximum effect often occurred 1 to 2 days after the peak of pollution. Summer pollution was associated with symptoms in the total population. No ozone or oxidant concentrations were monitored.

concentrations are insufficient for hospital admissions, with no clear separation of oxidant effects from effects of other pollutants. The effects of social factors, which produce day-of-week and weekly cyclical variations, and holiday and seasonal variations, are rarely removed (and then with possible loss of sensitivity). Attempts to relate time of visit to time of exposure are also very difficult. Any visit to medical facilities usually lacks appropriate denominators (the number of those at risk), since they are generally not available, and the catchment area is unknown (Bennett, 1981; Ward and Moschandreas, 1978). In addition, with the increased use of the emergency room as a family practice center, visits are becoming less associated with acute exposure or attack than they once were. Emergency room data, like hospital record data, often lack information on patients' smoking habits, ethnic group, social class, occupation, and even other medical conditions.

A study by Namekata et al. (1979) of emergency room visits for cardiac and respiratory diseases in two hospitals in Chicago must be considered inadequate because: (1) information collected from the medical records is insufficient to identify sources of variability in the data and to control for confounding factors of the types noted above; (2) the O_3 data are insufficient and incomplete; and (3) the linear models used could not determine effect levels of the pollutant.

Goldsmith et al. (1983) studied emergency room visits in four Southern California communities (Long Beach, Lennox, Azusa, and Riverside) during 1974-1975. Logbook data on total admissions were taken from two hospitals in each of the first three communities and from three hospitals in the fourth. The hospitals were $\leq$ 8 km from Southern California Air Quality Management District stations monitoring TSP, O_x, CO, NO, NO_2, SO_2, sulfate (SO_4), and aldehyde (COH). Catchment areas and air monitoring data from residential and work sites were unknown for the subjects included in the study. The data were adjusted for day-of-the-week and long-term trends, but not for seasonal trends. Maximum hourly averages of oxidants and temperature were reported to be associated with daily admissions in the high-oxidant area (Azusa) after correction for other variables using correlation coefficients from path analysis (although the more complete path analysis explained less variance than the standard regression model). Humidity had a positive effect and sulfates a negative effect when these variables were included in the model. Unfortunately, the lack of population denominators and characteristics, the lack of admission characteristics, and poor characterization of exposures seriously limit the use of these findings.

Bates and Sizto (1983) studied admissions to all 79 acute-care hospitals in Southern Ontario (i.e., the whole catchment area) during 4 months (January, February, July, August) in each year (1974, 1976-1978, and 1979-1980). Air pollution data for CO, NO_2, O_3, and COH were obtained from 15 stations mostly along the prevailing wind direction. Temperature was controlled. In July and August, highly significant associations (Pearson r, 1-tailed, $P \leq 0.001$) were found between excess (percent deviations from day-of-week and seasonal means) respiratory admissions and average maximum hourly SO_2 and O_3 (KI method) concentrations, and temperature (with 24- and 48-hr lags between the variables). Nonrespiratory admissions showed no relation to pollution. Ozone (maximum hourly average = 62.8 ppb) was independently related to admissions, as replicated in 1979 when SO_3 was greatly reduced. Temperature was also independently important (-5.3°C average on winter days in study). Admissions, and admission correlations with pollutants, were consistent from year to year. Further analysis showed that asthma was the most significant respiratory problem driving the admissions up, especially in younger people. Bronchitis and pneumonia admissions were not significantly related to pollutants. The authors state that effects of sulfates could not be separated from O_3 effects. Since the number of separate people admitted was unknown, a "sensitive" subpopulation could have affected the results. Improvements in the monitoring data (i.e., exposure) would help interpret these findings.

Whether changes in hospital use reflect changes in either illness experience or illness perception and behavior is still uncertain. A person may behave differently according to perceptions of environmental challenges. The response of the medical care system is also determined by several factors, including insurance and availability of physicians, beds, and services (Bennett, 1981; Ward and Monchandreas, 1978). Artifacts may arise from changing definitions of classifications and varying diagnostic or coding practices as well. Another frequent problem is that repeated admissions or attendance by a small number of patients can cause tremendous distortions in the data (Ward and Moschandreas, 1978). Furthermore, hospital statistics often lack reliability and validity since determining incidence is difficult, insufficient clinical data are available to support resolution of diagnostic category in grading severity, and a number of potential subclassifications of patients may require separation and attention in the analysis (Ward and Moschandreas, 1978).

12.3.1.7 Occupational Studies. Studies of acute effects from occupational exposure are summarized in Table 12-6. These studies did not meet the criteria necessary for developing quantitative exposure-response relationships for ambient ozone/oxidant exposures.

12.3.2 Trends in Mortality

The possible association between exposure to O_3 and increased mortality rates has been investigated a number of times, and the results have been reviewed at length in previous documents (National Research Council, 1977; U.S. Environmental Protection Agency, 1978; World Health Organization, 1978; Ferris, 1978). In 1978, the U.S. Environmental Protection Agency published data on the average number of deaths attributed to cardiac and respiratory causes among residents of Los Angeles County for different temperature ranges and days with low and high oxidant concentrations. This report suggested that a positive relationship might exist between oxidant exposure and mortality between 70° and 79°F. However, only five of the seven curves plotted from data in the range of 70° to 79°F have positive slopes. This proportion could show positive slopes simply by chance, with a probability of P = 0.16 by a sign test (as recalculated from the data), thus failing to support a relationship between oxidant concentrations and mortality. This failure is especially probable in light of the inconsistent slopes in the range of 80° to 89°F. Since high temperature and elevated oxidant concentrations tend to occur simultaneously in the Los Angeles Basin, Oechsli and Buechley (1970) studied the effects on mortality of heat waves among the elderly (in 1939, 1955, and 1963). They could not find evidence that high photochemical oxidant concentrations could augment the mortality effect of high temperature. Biersteker and Evendijk (1976) reached similar conclusions about heat-related mortality in July and August of 1975 and 1976 in Rotterdam, the Netherlands.

Sensitive subpopulations studied have included elderly residents of nursing homes and individuals with cardiopulmonary disease. The California Department of Public Health (1955, 1956, 1957) survey of nursing homes attempted to correlate daily mortality and patient transfers to the hospital with maximal daily temperatures and O_3 concentrations ($\geq$0.3 ppm). Heat had a significant effect on mortality, but no correlation could be found between mortality and high-O_3 days (Breslow and Goldsmith, 1958; Tucker, 1962).

TABLE 12-6. STUDIES OF ACUTE EFFECTS FROM OCCUPATIONAL EXPOSURE

Reference	Subject matter	Findings
Fabbri et al. (1979) Sarto et al. (1979a,b)	Pulmonary function in workers in a plastic bag factory (31 exposed and 31 controls of same age, height, smoking habits).	Decreased expiratory flow in 8 of 31 subjects at ozone levels of 196 to 1803 μg/m³ (0.10 to 0.92 ppm) during workshift. Lower flows in exposed smokers than control smokers. Acute changes to acetylcholinesterase, peroxidase, and lactate dehydrogenase. Other pollutants, including formaldehyde (0.18 to 0.20 ppm, 220 to 245 μg/m³), were not controlled.
Truche (1951)	Reported symptoms in tests of electric insulators with prolonged exposure to ozone >0.1 ppm.	Reports of thoracic cage constriction, inspiration difficulty, and laryngeal irritation. Other pollutants were not controlled.
Kleinfeld et al. (1957)	Clinical findings and symptoms in welders using inert gas-shield consumable electrodes in three plants with ozone measured at breathing zones.	Increase in chest constriction and throat irritation at 1-hr concentrations of 588 to 1568 μg/m³ (0.3 to 0.8 ppm); no complaints or clinical findings below 490 μg/m³ (0.25 ppm). Nitrogen dioxide and total suspended particulate matter were not measured or controlled.
Kudrjavceva (1963)	Symptoms in hydrogen peroxide production workers employed 7-10 years.	At 348 to 556 μg/m³ (0.25 to 0.40 ppm) headache, weakness, increased muscular excitability, and decreased memory. Other gases were possibly important.
Poloskaya (1968)	Symptoms in welders and nearby workers (controls) ages 25-35, with less than than 5 years employment.	More frequent complaints of respiratory irritation, headache, fatigue, and nosebleeds in welders; exams were normal. Ozone averaged 3332 μg/m³ (1.7 ppm), with maximum of 4900 μg/m³ (2.5 ppm); carbon monoxide and nitrogen dioxide were below permissible levels. Total suspended particulate matter was not studied.

TABLE 12-6. STUDIES OF ACUTE EFFECTS FROM OCCUPATIONAL EXPOSURE (continued)

Reference	Subject matter	Findings
von Nieding and Wagner (1980)	Health effects in male German metallurgical plant workers, as measured by questionnaire, absenteeism, insurance records, vital capacity measures, plethysmographic measures, blood pressure, and airway resistance. Ozone nitrogen oxides, and sulfur oxides were sampled.	Group exposed to high ozone had more absenteeism and more episodes of bronchitis and pneumonia, more cough and phlegm, and higher airway resistance than did controls. However, high total suspended particulate matter levels and temperature-induced volatilized metals obscured effects of ozone.
Oxhoj et al. (1979)	Pulmonary function in electric arc welders (n = 119, 5-38 years exposure) and clerical controls matched on smoking and age.	No acute effects found. Chronic pulmonary function changes thought to be related to particles only (not controlled).
Challen et al. (1958)	Symptoms in 14 helio-arc welders.	Upper respiratory symptoms in 11 of 14 welders exposed daily to ozone (0.8 to 1.7 ppm, 1568 to 3332 μg/ m^3), which disappeared with exposure to 392 μg/m^3 (0.2 ppm). Pulmonary congestion was seen at 3920 μg/m^3 (2 ppm). Nitrogen dioxide was present, but not studied.
Young et al. (1963)	Lung function in seven welders using argon-shield.	No changes in function from ozone (0.2 to 0.3 ppm, 392 to 588 μg/m^3). Nitrogen dioxide was probably present, but not controlled.
Nevskaja and Diterihs (1975)	Illness in hydrogen peroxide production workers measured by questionnaire and pulmonary function.	Increased prevalence of bronchitis and emphysema and decreased expiratory flow rates reported. Ozone concentrations were between 78 and 98 μg/m^3 (0.04 and 0.05 ppm) Sulfuric acid was also present.

Massey et al. (1961) compared daily mortality in two areas of Los Angeles County with similar temperatures but different photochemical pollution levels by multiple correlation and regression. No statistically significant relationships were observed. Buell et al. (1967) studied lung cancer mortality in different areas but could draw no meaningful conclusions. Mills (1957a,b) compared nursing home deaths with an index of photochemical pollution and found a positive association between the index and excess deaths; other investigators who analyzed the data observed no associations (California Department of Health, 1955, 1956, 1957; Breslow and Goldsmith, 1958). Studying the effect of pollution concentrations on cardiac and respiratory diseases in Los Angeles County, Hechter and Goldsmith (1961) found no significant correlation between pollutants and mortality, either on the same day or after 1 to 4 days of higher concentrations. Hechter and Goldsmith (1961) also failed to identify a contribution of oxidant levels to daily mortality in Los Angeles from 1962 to 1965.

12.4 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF CHRONIC EXPOSURE

Only a few prospective studies of the chronic effects of O_3 exposure are available. These studies are usually concerned with symptoms, lung function, chromosomal effects, and mortality rates. Mortality from chronic respiratory diseases and lung cancer has not been observed following oxidant exposures and is not likely to occur given the relatively low levels of oxidants and the proposed mechanisms of action.

12.4.1 Pulmonary Function and Chronic Lung Disease

Cohen et al. (1972) found no difference in ventilatory function or chronic respiratory symptoms in nonsmoking adults in the San Gabriel Valley and in San Diego, but their findings are limited by the similarity of annual average ambient levels of oxidants in the two areas. From 1963 through 1967 arithmetic mean oxidant levels were 0.047 ppm in San Gabriel Valley and 0.038 ppm in San Diego. Average daily maximum hourly oxidant levels during the period of the study were 0.12 ppm and 0.07 ppm, respectively, and other pollutants (TSP, SO_2, and RSP) were equivalent in both areas.

The University of California at Los Angeles (UCLA) population studies of chronic obstructive respiratory diseases in communities with different air pollutant exposures have been reported by Detels and colleagues (Detels et al., 1979; Rokaw et al., 1980; Detels et al., 1981). Three areas were exposed to photochemical oxidants (Burbank, CA); SO_x, particulates, and HCs (Long Beach, CA); and low levels of gaseous pollutants (Lancaster, CA). The prevalence of symptoms was reported to be increased in the residents of polluted areas. Lung function was generally better among residents of the low-pollution areas according to measurements of FEV_1, FVC, maximum expiratory flow rates, closing volume, thoracic volume, and airway resistance. Maximal mid-expiratory flow rate, considered to be sensitive to changes in small airways, was similar in all areas, while the mean ΔN_2 was slightly decreased among residents of the low-pollution areas. Although the results suggest that adverse effects of long-term exposure to photochemical oxidant pollutants may occur primarily in the larger airways, their usefulness is limited by a number of problems. For example, testing of subjects was not concurrent and occurred over a 4-year period between areas; the authors presented no information on such matters as self-selection and migration in and out of these areas.

Additional comparisons between mobile laboratory and hospital laboratory test results did not always show adequate reproducibility. The study populations had mixed ethnic groups, and completion rates were approximately 70 to 79 percent in the three areas. Comparisons of participants with census information were fairly close. Analysis of the comparisons of the three communities for symptoms and pulmonary function results used age- and sex-adjusted data only from white residents who had no history of change of occupation or residence because of breathing problems. Those with occupations that may have involved significant exposure were not necessarily excluded. Analyses were often made by smoking status and compared means or proportions that fell above or below certain levels.

A major difficulty in the analyses is that the exposure data presented are not adequate. Control of migration effects on chronic exposure was insufficient, and recent exposure information was provided only by ambient levels from only one monitor, located as far as 3 mi away. A further problem is that, as in most geographical comparisons, analysis of results assumes no differences by place, date, or season. This assumption is especially important since the study periods in each community were quite different. Furthermore, over the 4-year period of the study there were many changes, including amounts and types of cigarettes smoked, respiratory infection epidemics, and other undeterminable influences that could have affected the results. Also, the numbers of subjects changed from one report to another and from one analysis to another.

The major problem in interpreting the pulmonary function data is that the results do not appear to have been validated, as judged by the poor correlations between function and chronic symptoms and the fewer than expected smokers with abnormal lung function. In tests such as interpretation of flows at low lung volume or the single-breath nitrogen study, there do not appear to be appropriate comparisons for determining observer differences or biases, which are critical for these difficult tests.

Another major problem is that the investigators used cutoff points to examine the differences among the areas. Why cutoffs that were three to five standard deviations below the mean were chosen is unclear, especially since many of the variables examined were not normally distributed. By performing the analysis in the manner described, very few people were left with abnormalities in any group. Inconsistencies first surfaced when the authors examined such variables as total proportions of subjects with symptoms or the mean percent predicted lung function, and these inconsistencies grew worse. Furthermore, the method was inadequate to determine differences between one case in one area and two cases in another area. Insufficient numbers of cases were available, and the trends were in the wrong direction, especially those of the single-breath nitrogen ΔN_2. Whether the covariables and confounding variables were sufficiently handled in the analysis is not clear. Thus, this study must be treated as an insufficiently quantitative study for present purposes.

Additional studies of chronic morbidity are shown in Table 12-7. These studies also do not provide information useful for quantitative exposure-effect assessment. Thus, to date, insufficient information is available in the literature on possible exposure-effect relationships between O_3 and the prevalence of chronic lung disease. These relationships need further study.

12.4.2 Chromosomal Effects

The importance of chromosomal damage depends on whether the effect is mutagenic or cytogenetic, and, thus, whether it occurs in autosomal cells or peripheral lymphocytes. Translocations and trisomies are important forms of genetic damage, whereas minor chromosomal breakage (e.g., as associated with caffeine) are of questionable significance. Interest in chromosomal damage

TABLE 12-7. ADDITIONAL STUDIES OF CHRONIC MORBIDITY

Reference	Subject matter	Findings
California State Department of Public Health (1955-57)	Illness onsets throughout California in various age groups, measured by weekly surveys.	No relationship between incidence of illness and area in the young. Elderly showed some increases in Los Angeles. Pollutants other than ozone were also higher.
Hausknecht (1960, 1962)	Prevalence of illness in survey of 3445 households throughout California. Chronic pulmonary disease studied four times, 1957-1959.	Higher prevalence rates in Los Angeles and San Diego. No quantitative ozone data.
Deane et al. (1965), Goldsmith and Deane (1965)	Symptoms, measured by questionnaire and ventilatory function, in outdoor telephone workers 40-59 years of age in San Francisco and Los Angeles.	No differences in symptom prevalence between cities, although particulate concentrations were about twice as high in Los Angeles. No aerometric data.
Peters et al. (1973)	Illness in 61 welders, 63 pipefitters, 61 pipecoverers, and 94 new pipefitters, measured by questionnaires, pulmonary function, partial physicals, and X-rays.	Lung function obstruction in smokers in first two groups; third group had restrictive function. Otherwise, no differences were observed. Many pollutants were also involved.
Linn et al. (1976)	Respiratory symptoms and function in office-workers in Los Angeles and San Francisco, Summer of 1973.	No difference in chronic respiratory symptom prevalence between cities. More frequent reports of nonpersistent (<2 years) production of cough and sputum by women in the more polluted community. Different populations and different aerometric characteristics complicate the analysis.
Ulrich et al. (1980)	Immunological values in 30 workers (mean age 34) exposed for 2 to 9 years (mean of 4.3) to ozone, compared to reference values.	Increased immunoglobulins (IgG, IgA, and IgM), transferrin α, antitrypsin, apparently associated with 39 to 588 $\mu g/m^3$ (0.02 to 0.3 ppm). Other pollutants were not evaluated.

from O_3 derives from in vitro and in vivo studies (Chapter 10). Findings in in vivo human studies are conflicting, but generally negative (Chapter 11).

Four epidemiological studies have investigated chromosomal changes in humans exposed to O_3. None indicate any evidence that O_3 affects peripheral lymphocytic chromosomes in humans at the reported ambient concentrations. For example, Scott and Burkart (1978) studied chromosome lesions in peripheral lymphocytes of students exposed to air pollutants in Los Angeles. In their study of 256 college students who were followed continuously, they found chromosomal changes that were almost entirely of the simple-breakage type and not more numerous than is usual in a population study.

Magie et al. (1982) studied chromosome aberrations and peripheral lymphocytes in college students: 209 nonsmoking freshmen at a campus with higher smog levels (≥ 0.08 ppm O_3; ≥ 160 $\mu g/m^3$) and 206 freshmen at a campus with lower smog levels (<0.08 ppm O_3; <160 $\mu g/m^3$). Both campuses were located in Los Angeles. Students were enrolled in the study after completing questionnaires, and were assigned to groups on the basis of campus and previous residence. Blood samples and medical histories (obtained at the beginning of the school year, in November, in April, and at the beginning of the next school year) were analyzed for chromosome and chromatid aberrations, but no significant effects were found for chromosomal structure of peripheral lymphocytes.

Bloom (1979) studied military recruits before and after welding training. No effects were seen (O_3 levels were negligible and NO_2 was high). Fredga et al. (1982) studied the incidence of chromosome changes in men occupationally exposed to automobile fuels and exhaust gases in groups of drivers, automobile inspectors, and a reference group matched with respect to age, smoking habits, and length of job employment. Chromosome preparations from lymphocytes were made and analyzed by standardized routine methods. Analysis of the data gave no evidence for an occupational effect.

12.5 SUMMARY AND CONCLUSIONS

Field and epidemiological studies, when properly executed, offer a unique view of health effects research because they involve the real world, i.e., the study of human populations in their natural setting. However, these studies also have attendant limitations that must be considered in a critical evaluation of their results. One major problem in singling out the effects of one pollutant in field studies of either morbidity or mortality in populations has been the interference of other critical variables in the environment. Limitations also exist for epidemiological research on the health effects of oxidants, including interference or interaction between oxidants and other pollutants; meteorological factors such as temperature; proper exposure assessments including individual activity patterns and location of pollutant monitors; difficulty in identifying oxidant species responsible for observed effects; and characteristics of the populations such as hygiene practices, smoking habits, and socioeconomic status.

Investigative approaches comparing communities with high O_3 concentrations and communities with low O_3 concentrations have usually been unsuccessful, often because actual pollutant levels have not differed enough during the study and other important variables have not been adequately controlled. The terms "oxidant" and "ozone" and their association with health effects are often insufficiently clarified. Moreover, our knowledge about the measurement and calibration methods used is still lacking. Also, as our knowledge and skills in epidemiology improve, the incorporation of new key variables into the analyses is required. Thus, the incorporation of individual exposure data (e.g., from the home and workplace) becomes more of a necessity.

Both acute and chronic exposure situations have been reported in the literature on photochemical oxidants. Relevant studies providing quantitative information on effects associated with acute exposure include those on irritative symptoms, pulmonary function, and aggravation of existing respiratory disease (Table 12-8). A few studies, of limited quality, have been reported on morbidity, mortality, and chromosomal effects from chronic exposures.

Studies on the irritative effects of O_3 have been complicated by the presence of other photochemical oxidants and their precursors in the ambient environment. That O_3 causes the eye irritation normally associated with smog is doubtful. Nevertheless, studies indicate that eye irritation is likely to occur at oxidant levels of about 0.10 ppm. A shown in Table 12-8, associations between oxidant levels and symptoms such as eye, nose, and throat irritation, chest discomfort, cough, and headache have been reported at >0.10 ppm in both children and young adults (Hammer et al., 1974; Makino and Mizoguchi, 1975; Okawada et al., 1979). Zagraniski et al. (1979) also reported an association of these symptoms with approximately 157 $\mu g/m^3$ (0.08 ppm) ozone in adults with

TABLE 12-8. SUMMARY TABLE: ACUTE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS IN POPULATION STUDIES[a]

Lowest estimated effect level, ppm	Average maximum hourly concentration range during study, ppm	Observed effect(s)	Subjects	Reference
OXIDANTS				
b	0.03-0.15	Daily asthma attack rates increased on days with high oxidant and particulate levels and on cool days during a 34-week period in Los Angeles.	Juvenile and adult asthmatics	Whittemore and Korn, 1980
0.10	0.02-0.21	Eye irritation incidence rates increased with oxidant concentration.	Adolescents	Okawada et al., 1979
0.10[c]	<0.23	Symptoms of eye irritation, sore throat, headache, and cough related to oxidant concentration and temperature but not SO_2, NO_2, or NO.	Children and adolescents	Makino and Mizoguchi, 1975
0.10-0.15[c]	<0.04-0.50	Symptoms of eye irritation, cough, chest discomfort, and headache related to oxidant concentration but not carbon monoxide, nitrogen dioxide, or daily minimum temperature.	Young adults	Hammer et al., 1974
0.12[d]	0.06-0.37	Impaired athletic performance related to oxidant concentration but not nitrogen oxide, carbon monoxide, or particulate levels 1 hr before cross-country track meets in Los Angeles.	Adolescents	Wayne et al., 1967 Herman, 1972

TABLE 12-8. SUMMARY TABLE: ACUTE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS IN POPULATION STUDIES[a] (continued)

Lowest estimated effect level, ppm	Average maximum hourly concentration range during study, ppm	Observed effect(s)	Subjects	Reference
OZONE				
0.08	0.004-0.235	Increased daily prevalence rates for cough, eye, and nose irritation in smokers and patients with predisposing illnesses; pH of particulate was associated with eye, nose, and throat irritation while suspended sulfates were not associated with any symptoms.	Asthma and allergy patients; normal adults	Zagraniski et al., 1979
0.08	0.01-0.12	Daily peak flows decreased 12.2 to 14.8% with ozone and total suspended particulate matter.	Children and young adults	Lebowitz et al., 1982a, 1983 Lebowitz, 1984
0.08	0.01-0.12	Decreased daily peak flows and increased prevalence rate for acute symptoms associated with ozone, low temperature, and high total suspended particulate matter.	Adult asthmatics	Lebowitz et al., 1982a, 1983 Lebowitz, 1984
0.15	0.01-0.30	Increased airway resistance associated with ozone, sulfur dioxide, and temperature.	Adolescents	Kagawa and Toyoma, 1975 Kagawa et al., 1976; Kagawa, 1983
0.16[e]	0.16-0.17	Small decrement in forced expiratory function and increased symptoms with exercise in both normals and asthmatics.	Normal and asthmatic adults	Linn et al., 1980, 1983

[a] Ranked by lowest estimated effect level for oxidant or ozone.

[b] Not determined.

[c] U.S. Environmental Protection Agency, 1978.

[d] Hasselblad et al., 1976.

[e] Daily mean concentration of ozone was monitored by ultraviolet photometry inside a mobile laboratory; Linn et al., 1980, report concentrations multiplied by 1.25 that correspond to the neutral buffered potassium iodide (KI) method.

asthma and allergies. Discomfort caused by irritative symptoms may be responsible for the impairment of athletic performance reported in high school students during cross-country track meets in Los Angeles (Wayne et al., 1967; Herman, 1972). Although several additional studies have shown respiratory irritation apparently related to ambient exposure in community populations, none of these studies provide satisfactory quantitative data on acute respiratory illnesses.

Acute epidemiological studies in children and young adults have suggested that decreased peak flow and increased airway resistance occur over the range of O_3 concentrations from 157 to 294 $\mu g/m^3$ (0.08 to 0.15 ppm) (Kagawa and Toyoma, 1975; Kagawa et al., 1976; Kagawa, 1983; Lebowitz et al., 1982a, 1983; Lebowitz, 1984). Qualitative studies support this finding (McMillan et al., 1969; Lebowitz et al., 1974; Fabbri et al., 1979). No controlled human exposure studies in children are presently available for comparison, although studies in adults appear to show no effect below 235 $\mu g/m^3$ (0.12 ppm) O_3 (Chapter 11).

In studies of exacerbation of asthma and chronic lung diseases, the major problems in most of the studies have been the lack of information on the possible effects of medications, the absence of records for all days on which symptoms could have occurred, and the possible concurrence of symptomatic attacks. Investigators who have been able to control some of these variables have found consistent effects of O_3 on asthma (Table 12-8). Their findings have been in accordance with those of some of the earlier, more qualitative studies. Whittemore and Korn (1980) found small increases in the probability of asthma attacks associated with increases of 0.10 ppm in oxidant levels. Zagraniski et al. (1979) reported an increased prevalence rate for respiratory symptoms with approximately 157 $\mu g/m^3$ (0.08 ppm) O_3 in patients with asthma. Linn et al. (1980, 1983) found decreased pulmonary function and increased symptoms in lightly exercising asthmatics exposed to 314 to 333 $\mu g/m^3$ (0.016 to 0.17 ppm) O_3 or greater, regardless of other pollutants. With increased exercise levels, small effects were found at 235 $\mu g/m^3$ (0.12 ppm) O_3. Lebowitz et al. (1982a, 1983) and Lebowitz (1984) showed effects in asthmatics, related also to temperature, at O_3 levels of 102 to 235 $\mu g/m^3$ (0.052 to 0.12 ppm). There have been no consistent findings of symptom aggravation or changes in lung function in patients with other chronic lung diseases besides asthma.

Apparent adaptations have been observed under controlled conditions with humans, but this effect would be difficult to demonstrate in community populations. Recent work with animals suggests that the processes involved in adaptation may lead to other, perhaps adverse effects, but no implications for human health can yet be drawn.

Although animal studies indicate that O_3 impairs defenses against infection (Chapter 10), this impairment has not been examined in clinical studies. No positive studies of O_3 effects on acute respiratory illnesses have been reported in human populations. In addition, most studies have yet to address the hypothesis that years or decades of air pollution exposures beginning in childhood, especially among the sensitive, may increase the risk of developing chronic illness (U.S. Environmental Protection Agency, 1978).

The lack of quantitative measures of oxidant levels limits the usefulness of many studies of pollution exposure and mortality. In addition, properly designed studies have not been conducted to address the effects of oxidants on the growth and development of the lung or on the progression of chronic diseases, although the available evidence is consistent with toxicological data indicating that O_3 is not a strong mutagen or a demonstrable carcinogen at ambient concentrations. Most long-term studies have employed average annual levels or have involved broad ranges of pollution; others have used a simple high-oxidant/low-oxidant dichotomy and compared mortality results. Failure to relate mortality to specific levels (and types) of oxidant pollutants makes formulation of exposure-response relationships impossible. Epidemiological identification of chronic effects of air pollution generally requires well-conducted replicated studies of large, well-defined populations over long periods of time, which are not available at this time for O_3 or other photochemical oxidants.

Studies using quantitative measures find that "ozone alerts" occur frequently in association with high temperature. The latter may mask O_3 effects or by itself produce excess mortality in susceptible elderly cardiopulmonary patients. When attempts have been made to distinguish the effects of O_3, no positive relationship has been found with mortality; rather, the effect correlates most closely with elevated temperature.

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13. EVALUATION OF INTEGRATED HEALTH EFFECTS DATA FOR OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

13.1 INTRODUCTION

The preceding chapters (chapters 10, 11, and 12) have documented a wide array of toxicological responses elicited _in vivo_ and _in vitro_ by exposures to ozone at concentrations of 1 ppm and below and to other photochemical oxidants at various concentrations. The extensive body of data on the effects of ozone on the respiratory system was reported and discussed in particular detail in those chapters. The present chapter provides a vehicle for evaluating this collective body of data for its significance to public health and for assessing the certainties and uncertainties associated with the data. Since the purpose of a criteria document is to provide a scientific basis for the derivation and promulgation of standards, the present chapter addresses specific issues and questions that are important in standard-setting.

Paramount among the issues considered in standard-setting is the identification of the population or subpopulation to be protected by the regulation, that is, one that is at particular risk from exposure to ozone and other photochemical oxidants. The identification of such a population or subpopulation presupposes the identification of one or more effects that are in and of themselves adverse, or that are indicators of other effects that are adverse but that are not measurable in man because of ethical constraints.

The existing health effects data indicate that the responses to ozone and other photochemical oxidants that are most clearly linked to the potential impairment of public health are those changes in pulmonary function and related respiratory system variables that have been observed in human controlled-exposure studies and in a limited number of epidemiological studies. As discussed in the 1978 criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978), changes in lung function associated with exposure to ozone and other photochemical oxidants are viewed as signalling impairment of public health for several reasons. Decrements in the mechanical functions of the lung can interfere with normal activity in the general population and in susceptible subpopulations, depending upon the activity and the population. Even in the general population, ozone exposure during exercise can produce significant decrements in lung function (chapter 11). In certain individuals in the general population, not yet characterized medically except for their responses to ozone, significant decrements, larger than those seen in the rest of the general population, are elicited by exposure to ozone during either continuous or intermittent exercise (chapter 11). In individuals who have respiratory diseases such as asthma or chronic obstructive lung disease, even small decrements in lung function may interfere with normal activity and may be deemed clinically significant. Symptoms usually accompany the observed decrements in lung function and impairments in other respiratory indicators (chapters 11 and 12). Discomfort produced by the symptoms that ozone exposure produces have been reported as interfering with experimental protocols, especially those employing exercise.

> Thus, at least when associated with ozone exposure, changes in lung function often represent a level of discomfort that, even among healthy people, may restrict normal activity or impair the performance of tasks (U.S. Environmental Protection Agency, 1978).

To evaluate the health effects documented and described in the preceding chapters, relevant effects and the identification of potentially-at-risk populations are discussed at length in this chapter. In addition, inherent biological characteristics or personal habits and activities that may attenuate or potentiate typical responses to ozone and other oxidants are discussed. The environmental factors that determine potential or real exposures of populations or subpopulations are presented, as well, including known ambient air concentrations of ozone, of other related photochemical oxidants, and of these combined oxidants.

The issues discussed in subsequent sections are enumerated below:

1. Concentrations and patterns of ozone and other photochemical oxidants, including indoor-outdoor gradients, relevant for exposure assessment.
2. Symptomatic effects of ozone and other photochemical oxidants.
3. Effects of ozone on pulmonary function and related airway parameters in the general population, at rest and with exercise and other stresses.
4. Influence on the effects of ozone of age, sex, smoking status, nutritional status, and red blood cell enzyme deficiencies.
5. Effects of repeated exposure to ozone.
6. Effects of ozone on lung structure and the relationship between acute and chronic ozone effects.

7. Effects of ozone related to resistance to infections, i.e., host defense mechanisms.
8. Effects of ozone on extrapulmonary tissues, organs, and systems.
9. Effects of ozone on potentially susceptible individuals.
10. Extrapolation to human populations of ozone-oxidant effects observed in animals.
11. Effects of other photochemical oxidants and the interactions of ozone and other pollutants.
12. Identification of potentially-at-risk populations or subpopulations.
13. Demographic information on potentially at-risk subpopulations.

13.2 EXPOSURE ASPECTS

Certain information about the occurrence of ozone and other photochemical oxidants is important for assessing both the potential and the actual exposures of individuals and of populations. In this section, both qualitative and quantitative information is summarized as background for understanding the relevance for public health of the concentrations at which effects have been observed in health studies and as background for estimating exposures.

13.2.1 Exposures to Ozone

Ozone concentrations exhibit fairly strong diurnal and seasonal cycles. In most urban areas, single or multiple peaks of ozone occur during daylight hours, usually during midday (e.g., about noon until 3:00 or 4:00 p.m.). The formation of ozone and other photochemical oxidants is limited to daylight hours since the chemical reactions in the atmosphere are driven by sunlight. Because of the intensity of sunlight necessary and the other meteorological and climatic conditions required, the highest concentrations of ozone and other photochemical oxidants occur during the second and third quarters of the year, i.e., April through September. The months of highest ozone concentrations depend upon local or regional weather patterns to a considerable degree, such that the time of occurrence of maximum 1-hour, 1-month, or seasonal ozone concentrations is location-dependent. In California, for example, October is usually a month of higher ozone concentrations than April, and therefore the 6-month period of highest average ozone concentrations appears to be May through October in many California cities and conurbations.

In nonurban areas, most peaks in ozone concentrations occur during daylight hours, but peak concentrations at night are not uncommon. The occurrence of nighttime peaks appears to be the result of combined induction time and transport time for urban plumes, coupled with the lack of nitric oxide (NO) sources to provide NO for chemical scavenging of ozone in the evening and early morning hours. In nonurban areas, ozone concentrations are generally lower than in urban areas, but it is not unusual to encounter concentrations higher than those found in urban-core source areas or even in the suburbs of urban areas.

In urban areas, early morning ozone concentrations (around 2:00 or 3:00 a.m. until about 6:00 a.m.) are near zero (<0.02 ppm), largely because of scavenging by NO. Early morning ozone concentrations in nonurban areas are higher than in urban areas and are near background levels (e.g., 0.02 to 0.04 ppm), since surface scavenging rather than chemical scavenging by NO is the principal removal mechanism in nonurban areas.

Concentrations of ozone and the patterns of its occurrence are documented in chapter 6. Major points pertinent to exposure assessment have been described qualitatively above. Quantitative data are briefly summarized here. Figure 13-1 shows the frequency distribution of the three highest ozone concentrations for each of 3 years averaged together (1979 through 1981) (U.S. Environmental Protection Agency, SAROAD data file). The present national ambient air quality standard for ozone is expressed as a concentration not to be exceeded on more than one day per year. Thus, the second-highest 1-hour ozone concentration, rather than the highest, is regarded as a concentration of potential significance for public health. As demonstrated by this figure, 50 percent of the monitoring stations reported second-highest ozone concentrations, averaged over 3 years, of 0.12 ppm; 25 percent had 3-year-average second-highest ozone concentrations of 0.15 ppm; and 10 percent had 3-year-average second-highest ozone concentrations of 0.20 ppm. Since most of the ozone monitoring stations are located in urban areas (centers of greatest population density), the data cited above reflect the potential exposures to ozone of urban populations.

As data in chapter 11 and in section 13.3.4 show, human controlled-exposure studies have demonstrated that attenuation of responses to ozone during repeated, consecutive-day exposures of at least 3 to 4 days can occur in most, though not all, of the individuals studied. Thus, the potential for

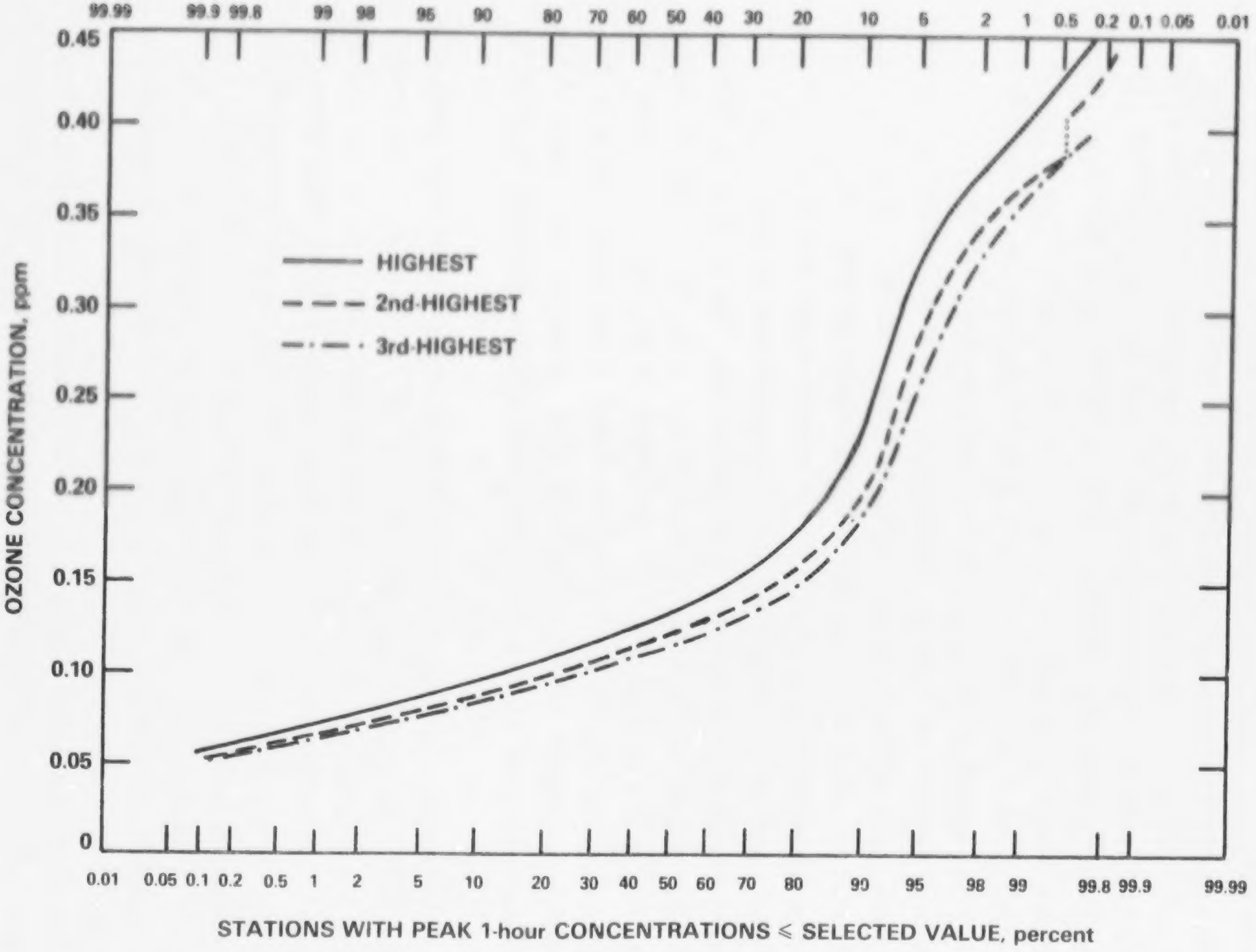

Figure 13-1. Collective distributions of the three highest 1-hour ozone concentrations for 3 years (1979, 1980, and 1981) at valid sites (906 station-years).

Source: U.S. Environmental Protection Agency, SAROAD data files for 1979, 1980, 1981.

repeated, consecutive-day exposures of that duration to ambient air concentrations of ozone is of interest. Data records from four cities were examined in chapter 6 for exposures to three different concentrations persisting for 3 consecutive days or longer (see Figures 6-23 through 6-26). Those data indicate the probabilities of exposures lasting n-days or longer, as shown in Table 13-1. As needed for exposure assessment, the consecutive days between multiple-day occurrences of these concentrations can be estimated from Figures 6-23 through 6-26 (chapter 6). Probabilities given in Table 13-1 are descriptive statistics based on aerometric data from the respective localities for 1979, 1980, and 1981. The data cannot be used to predict concentrations but indicate only the probable duration once a concentration has been reached.

Potential exposures of nonurban populations, while not easily ascertained in the absence of a suitable aerometric data base, can be estimated from aerometric data for selected sites known to represent agriculturally oriented areas and from aerometric data obtained from special-purpose monitoring networks. Data from three National Forest (NF) monitoring stations of the National Air Pollution Background Network (NAPBN) show 2-year averages of mean concentrations (1979 and 1980) of 0.028 ppm at Kisatchie NF, LA; 0.070 ppm at Custer NF, MT; and 0.110 ppm at Green Mt. NF, VT (Evans et al., 1982). (These are considered "nonurban" rather than remote or rural sites largely because they are thought to be subject to transport from urban areas at least some of the time. A documented case of transport for an NF site in Missouri is given in chapter 6.)

Data from Sulfate Regional Experiment (SURE) sites showed mean concentrations of ozone for August through December 1977 at four "rural" sites of 0.021, 0.029, 0.026, and 0.035 ppm at Montague, MA, Duncan Falls, OH, Giles County, TN, and Lewisburg, WV, respectively. At five "suburban" SURE sites (Scranton, PA; Indian River, DE; Rockport, IN; Ft. Wayne, IN; and Research Triangle Park, NC), mean concentrations for the study period were 0.023, 0.030, 0.025, 0.020, and 0.025 ppm, respectively. Maximum 1-hour ozone concentrations for the nine stations ranged from 0.077 ppm at Scranton, PA, to 0.153 ppm at Montague, MA (Martinez and Singh, 1979).

Concentrations of ozone indoors, since most people spend most of their time indoors, are of value in estimating total exposures. The estimation of total exposures, in turn, is of value for optimal interpretation and use of epidemiological studies. Data on concentrations of ozone indoors are few. It is known, however, that ozone decays fairly rapidly indoors through reactions

TABLE 13-1. PROBABILITY THAT SPECIFIED CONCENTRATIONS OF OZONE WILL PERSIST FOR STATED CONSECUTIVE DAYS OR LONGER[a]

(probability in percent)

Location	Persistence for stated no. of consecutive days or longer	% Probability for O_3 concentration of:	
		0.12 ppm	0.18 ppm
Pasadena, CA	2	72	59
	3	56	40
	4	42	29
	5	35	20
	6	28	16
	7	23	12
Pomona, CA	2	66	51
	3	50	34
	4	38	22
	5	30	15
	6	24	10
	7	19	7
		0.06 ppm	0.12 ppm
Washington, DC	2	49	—[b]
	3	33	—
	4	23	—
	5	16	—
	6	12	—
	7	9	—
Dallas, TX	2	77	22
	3	62	7
	4	50	~4
	5	40	~2
	6	32	<1
	7	24	<0.05

[a] Cumulative frequency distribution of concentrations by number of consecutive days of occurrence. Calculated from aerometric data for 1979 through 1981; not predictive of concentrations but only of probable duration.

[b] Few multiple-day occurrences in Washington and Dallas for higher concentrations; not plotted.

Source: Figures 6-23 through 6-26, Chapter 6, compiled from SAROAD data files for 1979 through 1981.

with surfaces of such materials as wall board, carpeting, and draperies (chapter 6). Ozone concentrations indoors depend also on those factors that affect both reactive and nonreactive pollutants: concentrations outdoors, air exchange rates, presence or absence of air conditioning, and mode of air conditioning (e.g., 100 percent fresh-air intake versus recirculation of air). Estimates in the literature on indoor-outdoor ratios (I/O, expressed as percent) of ozone concentrations range from 10 percent (Berk et al., 1981), for a residence, to 80 ± 10 percent (Sabersky et al., 1973), for an office building. Variations in estimates in the literature are attributable to the diversity of structures monitored, of their locations, and of their heating, ventilating, and air-conditioning systems.

Along with small-scale spatial variations in ozone concentrations, such as indoor-outdoor gradients, large-scale variations exist, such as those that occur with latitude. Latitudinal variations have little effect on potential exposures within the contiguous United States, however, since the contiguous states all fall within latitudes where photochemical oxidant formation is favored (Logan et al., 1981; U.S. Environmental Protection Agency, 1978).

Ozone concentrations are known to increase with altitude (Viezee et al., 1979; Seiler and Fishman, 1981). These gradients have no physiological significance for the general population, however, since concentrations are highest in the free troposphere, well above inhabited elevations. Data presented in chapter 6 (Table 6-6) for Denver show, in fact, that ozone concentrations are lower there than in many metropolitan areas of comparable size. These altitudinal gradients are of possible consequence, however, for certain high-altitude flights, as reported in the field studies documented in chapter 12. (Since pressure and other changes with altitude affect measurements and calibrations, care must be taken to ensure that ozone concentrations reported to produce health effects at real or simulated high altitudes are correct).

Despite the commonly accepted maxim that ozone is a regional pollutant, intermediate-scale spatial variations in concentrations occur that are of potential consequence for designing and interpreting epidemiological studies. For example, a study of ozone formation and transport in the northeast corridor (Smith, 1981) resulted in data showing that in New York City an appreciable gradient existed, at least for the study period (summer, 1980), between ozone concentrations in Brooklyn and those in the Bronx. The maximum 1-hour ozone concentration measured at the Brooklyn monitoring site was 0.174 ppm, while that measured at the Bronx monitoring site was 0.080 ppm.

13.2.2 Potential Exposures to Other Photochemical Oxidants

13.2.2.1 Concentrations. In chapter 6 of this document the ranges of concentrations of four photochemical oxidants other than ozone were presented for urban and, where possible, for nonurban atmospheres. The data presented in sections 6.6 and 6.7 are drawn upon here to examine possible ranges of these pollutants that might be encountered in the United States, including "worst-case" situations, in order to determine both the minimum and maximum additive concentrations of these pollutants with ozone likely to occur in ambient air. The four photochemical oxidants for which concentrations were given in sections 6.6 and 6.7 are peroxyacetyl nitrate, peroxypropionyl nitrate, hydrogen peroxide, and formic acid.

Although they co-occur to varying degrees with ozone, aldehydes are not photochemical oxidants. The concentrations of the low-molecular-weight aldehydes in ambient air are given in chapter 3 because these aldehydes are relatively potent precursors to ozone and other photochemical oxidants. Aldehydes are both primary and secondary pollutants, inasmuch as they are emitted directly to the atmosphere from certain sources and are also produced by atmospheric photochemical reactions. Since they are not oxidants and are not measured by methods that measure oxidants, their role relative to public health and welfare is not reported in this document. The reader is referred to a recent comprehensive review by Altshuller (1983) for a treatment of the relationships in ambient air between ozone and aldehyde concentrations.

Neither health effects data nor sufficient aerometric data on formic acid exist. Those ambient air concentrations that are given in the literature, however, indicate that formic acid occurs at trace concentrations, i.e., $\leq$0.015 ppm, even in high-oxidant areas such as the South Coast Air Basin of California (Tuazon et al., 1981). No data are available for other urban areas or for nonurban areas. Given the known atmospheric chemistry of formic acid, concentrations in the South Coast Air Basin are expected to be higher than in other urban areas of the country (chapter 4). More abundant aerometric data exist for the other three compounds and will be summarized in this section.

The measurement methods (IR and GC-ECD) for PAN and PPN are specific and highly sensitive, and have been in use in air pollution research for nearly two decades. Thus, the more recent literature on the concentrations of PAN and PPN confirm and extend, but do not contradict, earlier findings reported in the two previous criteria documents for ozone and other photochemical oxidants (U.S. Department of Health, Education, and Welfare, 1970; U.S. Environmental Protection Agency, 1978).

Concentrations of PAN are reported in the literature from 1960 through the present. The highest concentrations reported over this extended period were those found in the 1960s in the Los Angeles area: 70 ppb (1960), 214 ppb (1965); and 68 ppb (1968) (Renzetti and Bryan, 1961; Mayrsohn and Brooks, 1965; Lonneman et al., 1976).

The highest concentrations of PAN measured and reported in the past 5 years were 42 ppb at Riverside, California, in 1980 (Temple and Taylor, 1983), and 47 ppb at Claremont, California, also in 1980 (Grosjean, 1983). These are clearly the maximum concentrations of PAN reported for California and for the entire country in this period. Other recently measured PAN concentrations in the Los Angeles Basin were in the range of 10 to 20 ppb. Average concentrations of PAN in the Los Angeles Basin in the past 5 years ranged from 4 to 13 ppb (Tuazon et al., 1981; Grosjean, 1983). The only published report covering PAN concentrations outside California in the past 5 years is that of Lewis et al. (1983) for New Brunswick, New Jersey. The average PAN concentration was 0.5 ppb and the maximum was 11 ppb during a study done from September 1978 through May 1980. Studies outside California from the early 1970s through 1978 showed average PAN concentrations ranging from 0.4 ppb in Houston, Texas, in 1976 (Westberg et al., 1978) to 6.3 ppb in St. Louis, Missouri, in 1973 (Lonneman et al., 1976). Maximum PAN concentrations outside California for the same period ranged from 10 ppb in Dayton, Ohio, in 1974 (Spicer et al., 1976) to 25 ppb in St. Louis (Lonneman et al., 1976).

In Chapter 6, data on PPN concentrations from 1963 through the present were presented. The highest PPN concentration reported in these studies was 6 ppb in Riverside, California (Darley et al., 1963). The next highest reported PPN concentration was 5 ppb at St. Louis, Missouri, in 1973 (Lonneman et al., 1976). Among more recent data, maximum PPN concentrations at respective sites ranged from 0.07 ppb in Pittsburgh, Pennsylvania, in 1981 (Singh et al., 1982) to 3.1 ppb at Staten Island, New York (Singh et al., 1982). California concentrations fell within this range. Average PPN concentrations at the respective sites for the more recent data ranged from 0.05 ppb at Denver and Pittsburgh to 0.7 ppb at Los Angeles in 1979 (Singh et al., 1981).

Altshuller (1983) has succinctly summarized the nonurban concentrations of PAN and PPN by pointing out that they overlap the lower end of the range of urban concentrations at sites outside California. At remote locations, PAN and PPN concentrations are lower than even the lowest of the urban concentrations (by a factor of 3 to 4).

In urban areas, hydrogen peroxide (H_2O_2) concentrations have been reported to range from $\leq$ 0.5 ppb in Boulder, Colorado (Heikes et al., 1982) to $\leq$ 180 ppb in Riverside, California (Bufalini et al., 1972). In nonurban areas, reported concentrations ranged from 0.2 ppb near Boulder, Colorado, in 1978 (Kelly et al., 1979) to $\leq$ 7 ppb 54 km southeast of Tucson, Arizona (Farmer and Dawson, 1982). These nonurban data were obtained by the luminol chemiluminescence technique (see chapter 5). The urban data were obtained by a variety of methods, including the luminol chemiluminescence, the titanium (IV) sulfate 8-quinolinol, and other wet chemical methods (see chapter 5).

The higher concentrations of H_2O_2 reported in the literature must be regarded as especially problematic, since FTIR measurements of ambient air have not demonstrated unequivocally the presence of H_2O_2 even in the high-oxidant atmosphere of the Los Angeles area. The limit of detection for a 1-km-pathlength FTIR system is around 0.04 ppm (chapter 5); FTIR is capable of measuring concentrations of H_2O_2 if it is present above the limit of detection.

13.2.2.2 Patterns. The patterns of formic acid (HCOOH), PAN, PPN, and H_2O_2 may be summarized fairly succinctly. They bear qualitative but not quantitative resemblance to the patterns already summarized for ozone concentrations. Qualitatively, diurnal patterns are similar, with peak concentrations of each of these occurring in close proximity to the time of the ozone peak. The correspondence in time of day is not exact, but is close. As the work of Tuazon et al. (1981) at Claremont, California, demonstrates (see Figures 6-37 and 6-43), ozone concentrations return to baseline levels faster than the concentrations of PAN, HCOOH, or H_2O_2 (PPN was not measured). The diurnal patterns of PAN were reported in earlier criteria documents. Newer data merely confirm those patterns.

Seasonally, winter concentrations (third and fourth quarters) of PAN are lower than summer concentrations (second and third quarters). The winter concentrations of PAN are proportionally higher, however, than the winter concentrations of ozone; i.e., the PAN-to-ozone ratios are higher in winter than in summer. Data are not readily available on the seasonal patterns of the other non-ozone oxidants.

Indoor-outdoor data on PAN are limited to one report (Thompson et al., 1973), which confirms the pattern to be expected from the known chemistry of PAN; that is, it persists longer indoors than ozone. Data are lacking for the other non-ozone oxidants.

13.2.3 Potential Combined Exposures and Relationship of Ozone and Other Photochemical Oxidants

Data on concentrations of PAN, PPN, and H_2O_2 summarized in this section indicate that in "worst-case" situations these non-ozone oxidants together could add as much as about 0.15 ppm of oxidant to the ozone burden in ambient air. The highest second-high ozone concentration measured in the United States in 1982 was 0.32 ppm, in the Los Angeles area. In the presence of that concentration of ozone, the addition of non-ozone oxidants (0.15 ppm total) would bring the total oxidant concentration to around 0.47 ppm, provided the maximum concentrations of ozone and non-ozone oxidants were reached at the same time.

Data also indicate that at their average concentrations in recent years in the Los Angeles Basin, PAN and PPN together would add an additional oxidant burden of 14 ppb (0.014 ppm) (4 to 13 ppb average PAN: Tuazon et al., 1981; Grosjean, 1983, respectively; and 0.7 ppb PPN: Singh et al., 1981).

The significance for public health of the imposition of an additional oxidant burden from non-ozone oxidants rests, however, on the answers to at least three basic questions:

1. Do PAN, PPN, or H_2O_2, singly or in combination, elicit adverse or potentially adverse responses in human populations?
2. Do any or all of these non-ozone oxidants act additively or synergistically in combination with ozone to elicit adverse or potentially adverse responses in human populations? Do any or all act antagonistically with ozone?
3. Do the time course and magnitude of the concentrations of these non-ozone oxidants parallel the time course and magnitude of ozone concentrations in the ambient air?

The first two questions are addressed by health effects data presented in chapters 10 through 12 and in section 13.7 of the present chapter.

Altshuller (1983) has reviewed data pertinent to the third question. His conclusion is that "the ambient air measurements indicate that O_3 may serve directionally, but cannot be expected to serve quantitatively as a surrogate for the other products" (Altshuller, 1983). It must be emphasized here that Altshuller examined the issue of whether O_3 could serve as an abatement surrogate for all photochemical products, including those not relevant to effects data examined in this document. For example, the products be reviewed relative to ozone included aldehydes, aerosols, and nitric acid. Nevertheless, his conclusions appear to apply to the subset of photochemical products of concern here: PAN, PPN, and H_2O_2.

The most straightforward evidence of the lack of a quantitative, monotonic relationship between ozone and the other photochemical oxidants is the range of PAN-to-O_3 and, indirectly, of PAN-to-PPN ratios presented in the review by Altshuller (1983) and summarized in Table 13-2 and in chapter 6.

Certain other information presented in chapter 6 bears out the lack of a strict quantitative relationship between ozone and PAN, in particular. Not only are ozone-PAN relationships not consistent between different urban areas, but they are not consistent in urban versus nonurban areas, in summer versus winter, in indoor versus outdoor environments, or even, as the ratio data show, in location, timing, or magnitude of diurnal peak concentrations within the same city. Data obtained in Houston by Jorgen et al. (1978) show variations in peak concentrations of concurrently measured PAN among three separate monitoring sites. Temple and Taylor (1983) have shown that PAN concentrations are a greater percentage of ozone concentrations in winter than in the remainder of the year in California (see chapter 6). Lonneman et al. (1976) demonstrated that PAN-to-O_3 ratios are considerably lower in nonurban than in urban areas. Thompson et al. (1973) showed that PAN persists longer than ozone indoors. (This is to be expected from its lower reactivity with surfaces and its enhanced stability at cooler-than-ambient temperatures such as found in air-conditioned buildings.) Tuazon et al. (1981) demonstrated that PAN persists in ambient air longer than ozone, its persistence paralleling that of HNO_3, at least in some localities. Reactivity data presented in the 1978 criteria document for ozone and other photochemical oxidants indicate that all precursors that give rise to PAN also give rise to ozone. Not all are equally reactive toward both products, however, and therefore some precursors preferentially give rise, on the basis of units of product per unit of reactant, to more of one product than the other (U.S. Environmental Protection Agency, 1978).

TABLE 13-2. RELATIONSHIP OF OZONE AND PEROXYACETYL NITRATE AT URBAN AND SUBURBAN SITES IN THE UNITED STATES IN REPORTS PUBLISHED 1978 OR LATER

Site/year of study	PAN/O_3, % Avg.	 At O_3 peak	Reference
West Los Angeles, CA, 1978	9	6	Hanst et al. (1982)
Claremont, CA, 1978	7	6	Tuazon et al. (1981a, 1981b)
Claremont, CA, 1979	4	4	Tuazon et al. (1981a)
Riverside, CA, 1975-1976	9	5	Pitts and Grosjean (1979)
Riverside, CA, 1976	5	4	Tuazon et al. (1978)
Riverside, CA, 1977	4	4	Tuazon et al. (1980)
Riverside, CA, 1977	4	NA[a]	Singh et al. (1979)
Houston, TX, 1976	3	3	Westberg et al. (1978)
New Brunswick, NJ, 1978-1980	4	2	Brennan (1980)

[a] Not available.

Source: Derived from Altshuller (1983). For primary references, see chapter 6.

It must be emphasized that information presented in chapter 5 clearly shows that no one method can quantitatively and reliably measure ozone, PAN, PPN, and hydrogen peroxide, either one at a time or in ambient air mixtures. This point was not clearly presented in the 1978 criteria document but is given substantial discussion in chapter 5 of this document.

13.3 HEALTH EFFECTS IN THE GENERAL HUMAN POPULATION

13.3.1 Clinical Symptoms

A close association has been observed between the occurrence of respiratory symptoms and changes in pulmonary function in response to acute exposure to O_3 (Chapter 11). This association holds for both the time-course and magnitude of effects. In studies of repeated exposure to O_3, symptoms have generally increased while pulmonary function has diminished on the second to third day of exposure, followed by partial or complete reversal of these findings on the fourth or fifth day. Insofar as cough and chest pain or irritation may interfere with the maximal inspiratory or expiratory efforts required to perform spirometric maneuvers, such associations between symptoms and function might be expected. To date, epidemiological studies of the health effects of photochemical air pollution have not been designed specifically to test the comparative frequency or magnitude of response of symptoms versus functional changes. Which type of effect is more likely to occur within the polluted community is uncertain.

The symptoms found in association with clinical exposure to O_3 alone and with exposure to photochemical air pollution are similar but not identical. Eye irritation, one of the commonest complaints associated with photochemical pollution, is not characteristic of clinical exposures to O_3, even at concentrations of the gas several times higher than any likely to be encountered in ambient air. Other components of photochemical air pollution, such as aldehydes and PAN, are held to be chiefly responsible (National Air Pollution Control Association, 1970; Altshuller, 1977; National Research Council, 1977; U.S. Environmental Protection Agency, 1978; Okawada et al., 1979).

There is also evidence to suggest that for a specified concentration of O_3 other symptoms, as well, are more likely to occur in populations exposed to ambient air pollution than in subjects exposed in chamber studies, especially if O_3 is the sole pollutant administered in the chamber studies. The symptoms may be indicative of either upper or lower respiratory tract irritation. In epidemiological studies, cough has been reported at 0.08 ppm O_3 (Zagraniski et al., 1979) and at 0.10 ppm oxidants (Hammer et al., 1974; Makino and Mizoguchi, 1975). Some subjects have experienced cough during clinical exposure to 0.12 ppm O_3 (McDonnell et al., 1983). Nose and throat irritation have been reported in community studies in association with 0.10 ppm oxidants (Okawada et al., 1979; Makino and Mizoguchi, 1975), but not at or below 0.15 ppm O_3 in laboratory studies.

Between 0.15 and 0.30 ppm O_3, a variety of both respiratory and nonrespiratory symptoms have been reported in controlled exposures. They include throat dryness, difficulty or pain in inspiring deeply, chest tightness, substernal soreness or pain, wheezing, lassitude, malaise, and nausea (DeLucia and Adams, 1977; Kagawa and Tsuru, 1979b; McDonnell et al., 1983). Most "symptom scores" have been positive at concentrations of 0.2 ppm O_3 and above; only two studies reported finding no symptoms at 0.3 ppm O_3 (Bennett, 1962;

von Nieding et al., 1977). Symptoms tend to remit within hours after exposure is ended. Relatively few subjects have reported persistence of symptoms beyond 24 hours.

There are several possible explanations for the apparent differences in symptomatic effects between epidemiological and controlled human studies. They include differences in subject populations (e.g., children were subjects in two of the epidemiological studies but have not been studied clinically); factors affecting the perception of symptoms in one type of study compared to the other; or differences in the methods used to assess symptoms. Alternatively, the presence of highly reactive chemical species in polluted ambient air might be chiefly responsible for the symptoms or might interact synergistically with O_3 to initiate the symptoms.

Symptoms have commonly been assessed by the use of recording sheets combined with reliance on the subject's recall, usually right after exposure but sometimes several hours or days after exposure (e.g., community studies). While it is difficult to score the intensity of symptoms with confidence, the results obtained immediately after exposure have been noteworthy for their general consistency across studies. Moreover, as noted earlier, the association between changes in symptoms and objective functional tests has been impressive. Symptoms are therefore considered as useful adjuncts in assessing the effects of O_3 and photochemical pollution, particularly if combined with objective measurements.

13.3.2 Pulmonary Function at Rest and with Exercise and Other Stresses

13.3.2.1 At-Rest Exposures. The great majority of short-term ozone exposure studies on resting subjects were published almost a decade ago and were reviewed extensively in the previous ozone-oxidants criteria document (U.S. Environmental Protection Agency, 1978). Briefly, resting subjects inhaling ozone at concentrations up to 0.75 ppm for 2 hours showed no decrements or only very small (< 10 percent) decrements in FVC (Silverman et al., 1976; Folinsbee et al., 1975; Bates et al., 1972), vital capacity (Silverman et al., 1976; Folinsbee et al., 1975), FEV_1, and FRC (Silverman et al., 1976). More discriminating flow-derived variables, such as the maximal expiratory flow at 50 percent VC (FEF 50%) and the maximal expiratory flow at 25 percent VC (FEF25%), were affected to a greater degree, showing decreases of up to 30 percent from control in sensitive individuals at 0.75 ppm O_3 (Bates et al., 1972; Silverman et al., 1976). Specific tests for bronchoconstriction did not appear to be more sensitive in detecting ozone-induced changes than the spirometric tests. Airway resistance (R_{aw}) and pulmonary resistance (R_L) increased only minimally following 2-hr exposures to 0.6 to 0.75 ppm O_3 (Golden et al., 1978 and 0.75 ppm O_3 (Silverman et al., 1976). More specific measures of pulmonary mechanics exhibited a similar lack of response. Static compliance (C_{st}) remained virtually unchanged, whereas dynamic compliance (C_{dyn}) and the maximum static elastic recoil pressure of the lung ($P_{tp\ max}$) showed some borderline effects (Bates et al., 1972). No consistent effects of ozone were observed in the most sensitive region of the respiratory system, the gas-exchange zone of the lung. Breathing 0.6 to 0.8 ppm O_3 for 2 hr reduced markedly diffusion capacity (D_{Lco}) across the alveolo-capillary membrane (Young et al., 1964); however, the mean fractional CO uptake, also an index of diffusion, decreased only marginally under similar exposure conditions (Bates et al., 1972). The slope of phase III of the single-breath nitrogen closing volume curves, which increases as the inhomogeneity in the distribution of ventilation increases, was not significantly altered by O_3 inhalation (Silverman et al., 1976).

More recent studies of at-rest exposures to O_3 lasting 2 to 4 hr have demonstrated decrements (< 11 percent) in forced expiratory volume and flow occurring at and above 0.5 ppm of O_3 (Folinsbee et al., 1978; Horvath et al., 1979). Airway resistance was not changed at these O_3 concentrations. Breathing O_3 at rest at concentrations < 0.5 ppm did not significantly impair pulmonary function (Folinsbee et al., 1978), although the occurrence of some O_3-related pulmonary symptoms has been suggested (König et al., 1980), indicating that there may be selective sensitivity in some subjects.

13.3.2.2 Exposures With Exercise. Minute ventilation ($\dot{V}_E$) during exposure is considered to be one of the principal modifiers of the magnitude of response to O_3. The most convenient physiological procedure for increasing $\dot{V}_E$ is to exercise exposed individuals either on a treadmill or bicycle ergometer. Adjustment by the respiratory system to an increased work load is characterized by increased frequency and depth of breathing. Consequent increases in $\dot{V}_E$ not only increase the overall volume of inhaled pollutant, but such ventilatory patterns also promote a deeper penetration of ozone into the peripheral lung structures, which are most sensitive to injury and which favor a greater absorption of ozone. These processes are further enhanced at higher workloads

($\dot{V}_E$ > 35 L/min), since the mode of breathing will most likely change from nasal to oronasal or oral only (Niinimaa et al., 1980). Such a redistribution of the respiratory airflow, with an increasingly greater portion of the total minute volume being inhaled orally as the ventilation increases (Niinimaa et al., 1981), may proportionally augment the ozone burden of the airways. The overall amount of inhaled ozone depends on minute ventilation, ozone concentration, and duration of exposure. The effective dose of O_3, which is a composite index of these three determinants (Silverman et al., 1976; Folinsbee et al., 1978; Adams et al., 1981) can be used to predict group mean decrements in pulmonary function following O_3 exposure. However, considering the great variability in individual responses to O_3 exposure, prediction equations that use some form of effective dose may not be adequate for predicting differences in responsiveness to O_3 among individuals.

Even in well-controlled experiments on a homogenous group of subjects, physiological responses to the same work and pollutant loads will vary widely among individuals (Chapter 11). The nature of the primary mechanisms inducing such a spectrum of responses is unclear. Despite such large interindividual variability, the magnitude of (individual) responses, assessed in terms of decrements in pulmonary function, correlates reasonably well with the severity and frequency of subjective symptoms; but the positive association with both O_3 concentration and exercise stress is much stronger (Folinsbee et al., 1978; McDonnell et al., 1983; Haak et al., 1984). Generally, within-individual variations in response, both subjective and objective, appear to be almost an order of magnitude smaller than the variations observed between subjects.

The post hoc categorization of subjects into "responders/sensitives" and "nonresponders/nonsensitives" is based on arbitrary criteria that vary from study to study (Bell et al., 1977; Gliner et al., 1983; Haak et al., 1984) and is clearly open to criticism. Using this approach, up to 20 percent of subjects in the studies cited were classified as more reactive to ozone than the rest of the cohorts. Even under very strenuous exposure conditions ($\dot{V}_E$ = 45-57 L/min at 0.4 ppm), when lung function in the most responsive yet apparently healthy individuals was severely impaired (FEV_1=40 percent of control), the least responsive subjects showed decrements of less than 10 percent; and the average decrement was 26 percent (Haak et al., 1984; Silverman et al., 1976). Moderate exercise ($\dot{V}_E$ = 34 L/min) in an atmosphere containing 0.4 ppm ozone may reduce the average FEV_1 of healthy subjects by 17 percent (3 to 50 percent).

The same level of exercise in 0.24 ppm ozone elicits mean decreases in FVC, FEV_1, and FEF_{25-75} of 11, 14, and 12 percent, respectively. Even very low O_3 concentrations (0.12 ppm) will induce measurable changes in lung function of more responsive individuals; reported decrements in FVC, FEV_1 and FEF_{25-75} did not exceed 20 percent of control (McDonnell et al., 1983).

The maximum response can be observed within 5 to 10 min following the end of each exercise period (Folinsbee et al., 1977b; Haak et al., 1984). During subsequent rest periods, however, the augmented response is not maintained and partial improvement, but not a return to the preexercise level, in lung function can be observed even though the subject still inhales ozone (Folinsbee et al., 1977b). Continuous exercise equivalent in duration to the sum of intermittent exercise periods at comparable ozone concentrations (0.20 to 0.40 ppm) and minute ventilations (approximately 60 to 80 L/min) seems to elicit about the same changes in pulmonary function (Adams et al., 1981; Adams and Schelegle, 1983). Functional recovery, at least from a single exposure with exercise, appears to progress in two phases: during the initial rapid phase, lasting between 1 and 3 hours, pulmonary function improves more than 50 percent (Bates and Hazucha, 1973); this is followed by a much slower recovery that is usually completed within 24 hours. There is some indication, however, that recovery from sequential exposures may take longer than 24 hours (Folinsbee et al., 1980). In some individuals, despite apparent functional recovery, other regulatory systems may still exhibit abnormal responses when stimulated; e.g., airway hyperreactivity might persist for days (Golden et al., 1978; Kulle et al., 1982b).

In evaluating group response, the magnitude of lung functional changes is positively associated with the level of exercise and ozone concentration. Heavy intermittent exercise ($\dot{V}_E > 44$ L/min) at high ozone concentrations (0.4 to 0.6 ppm) significantly reduces FVC by more than 10 percent, FEV_1 by almost 20 percent, and FEF_{25-75} by nearly 30 percent, on the average. The comparable exercise stress at lower ozone concentrations (0.12 to 0.20) decreases the above lung function variables between 3 and 7 percent, with these decrements bordering on statistical significance.

The effects of intermittent exercise and O_3 concentration on the magnitude of average pulmonary function response (e.g., FEV_1) during 2-hr exposures are best illustrated in Figures 13-2 through 13-6. The data base for these concentration-response curves comprises studies published between 1973 and 1983

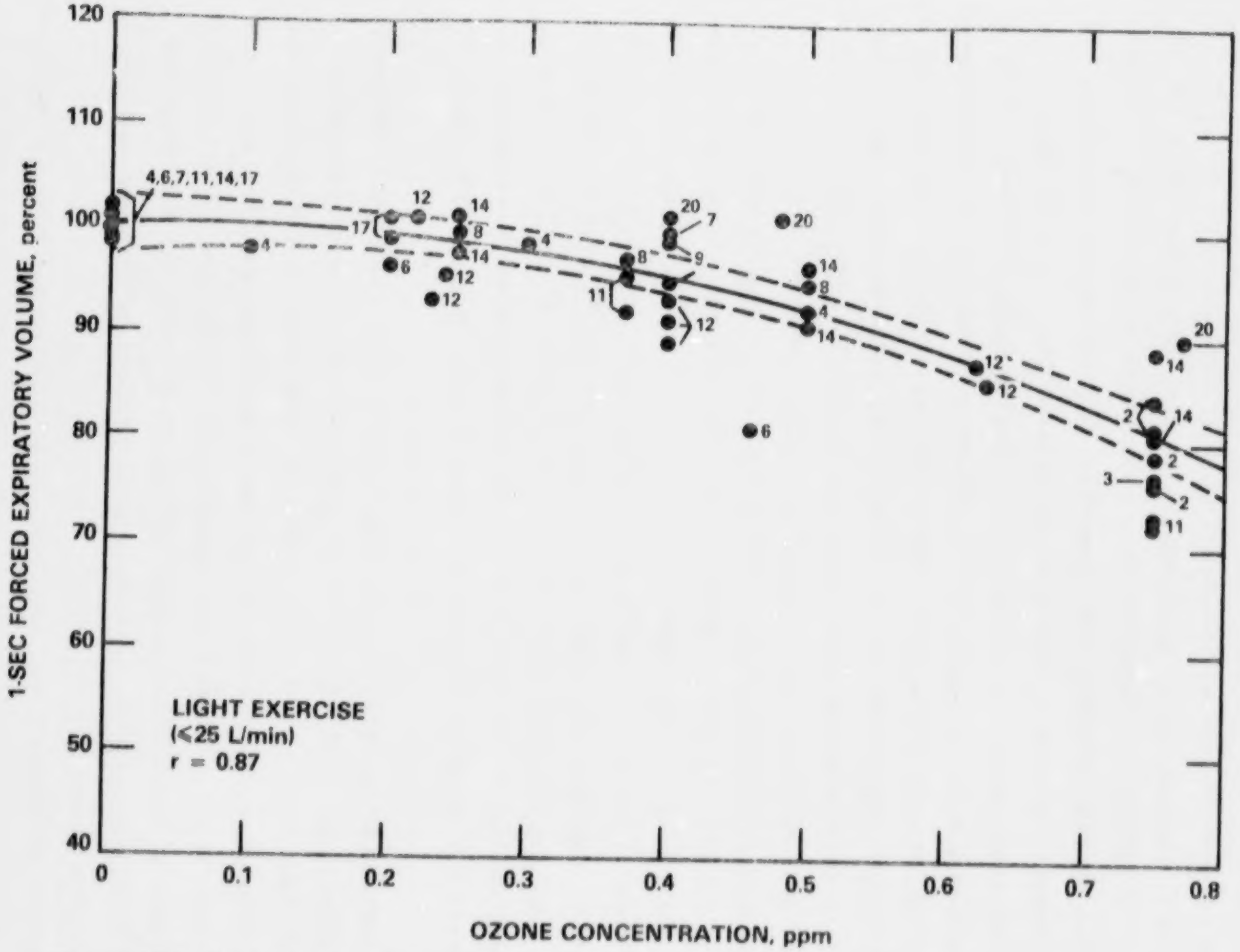

Figure 13-2. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with light intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 13-3 along with specific references.

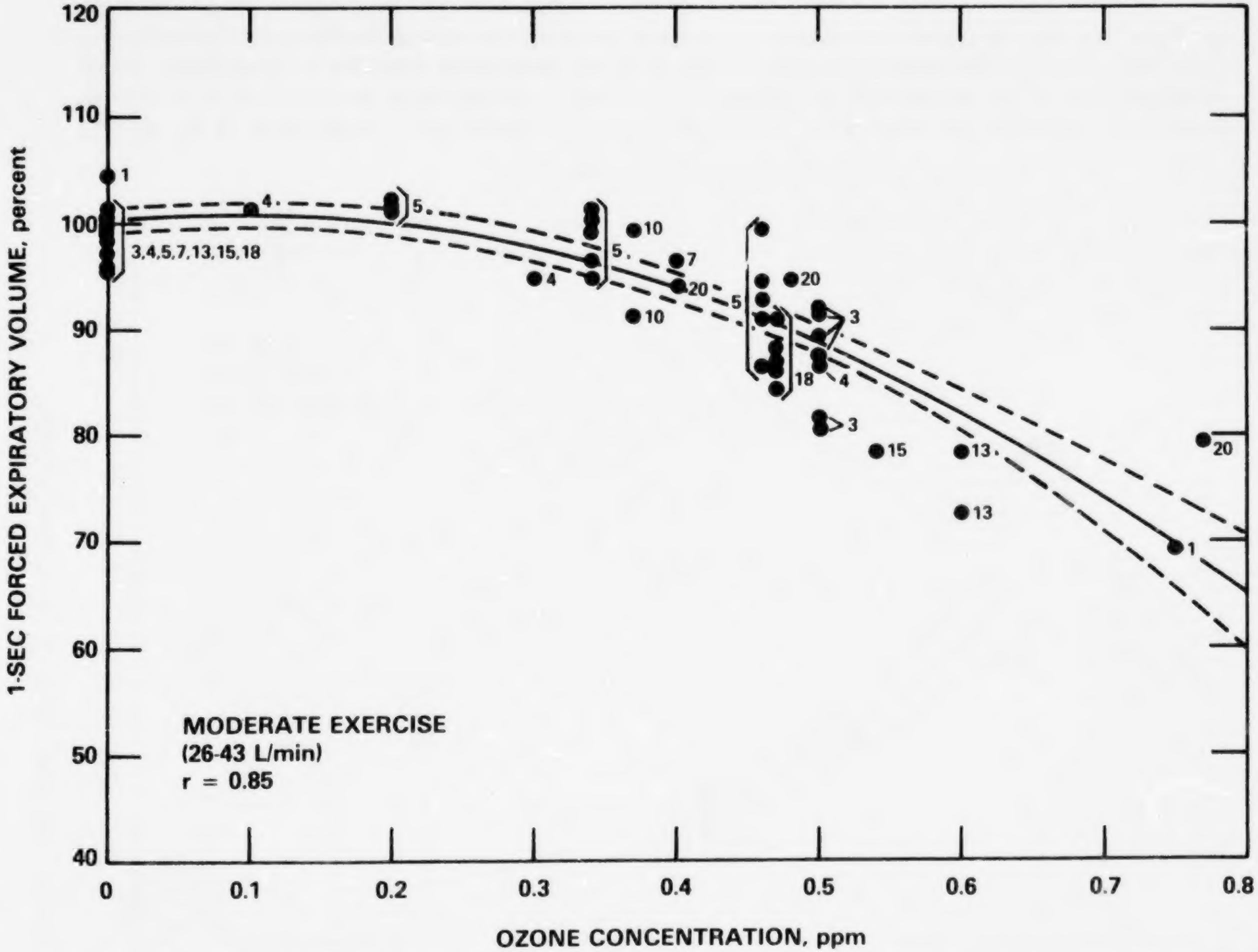

Figure 13-3. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with moderate intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 13-3 along with specific references.

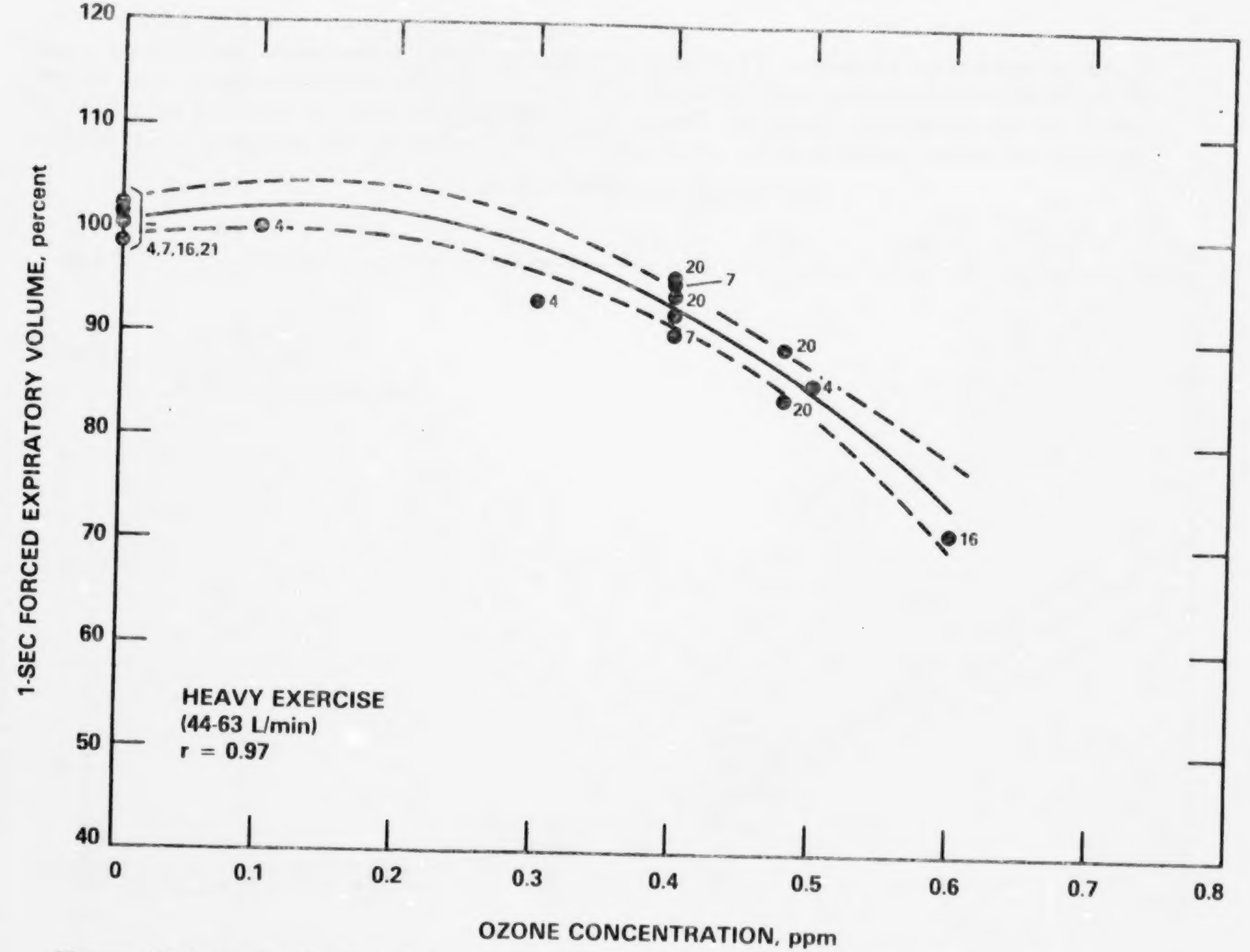

Figure 13-4. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 13-3 along with specific references.

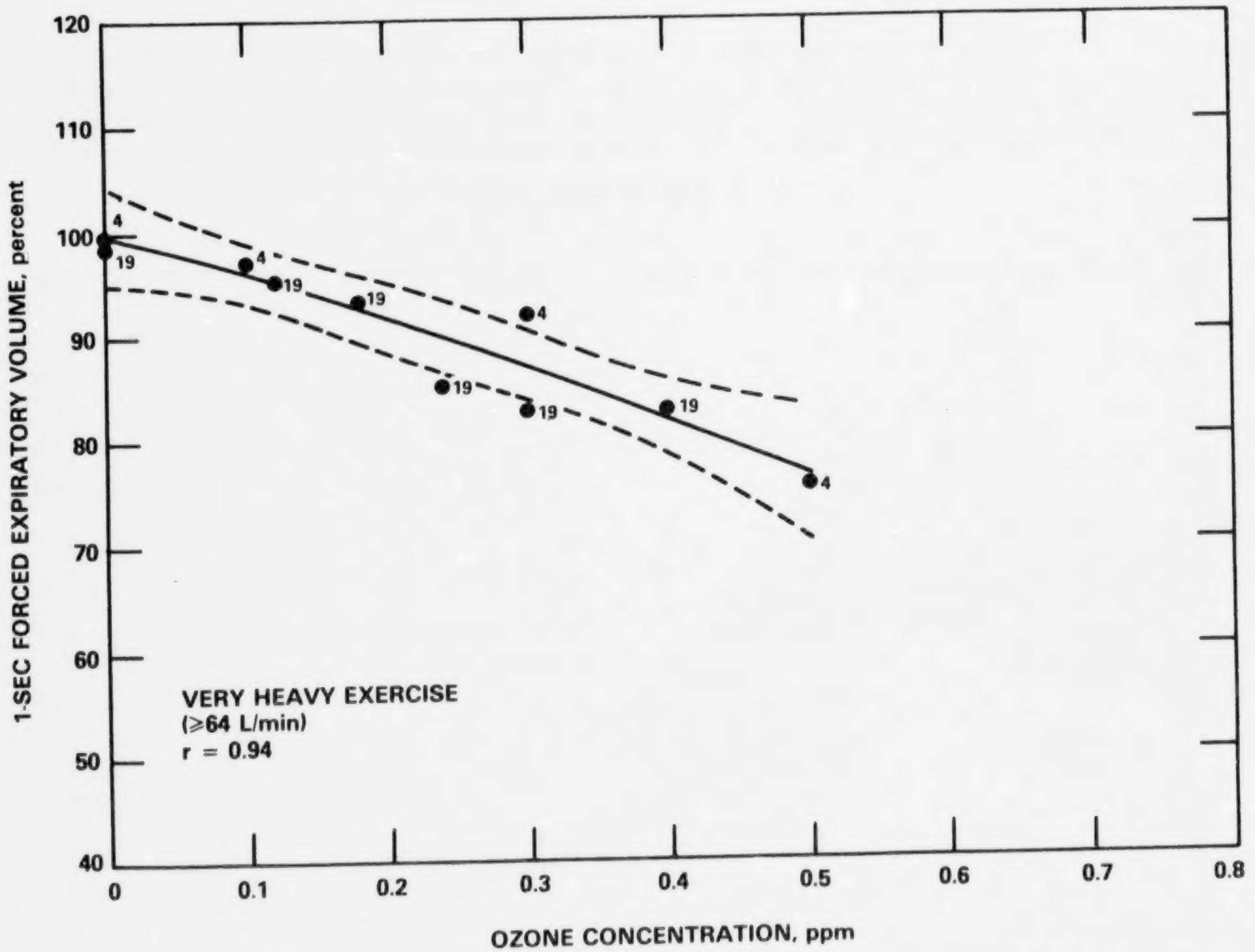

Figure 13-5. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with very heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (±standard error)are given in Table 13-3 along with specific references.

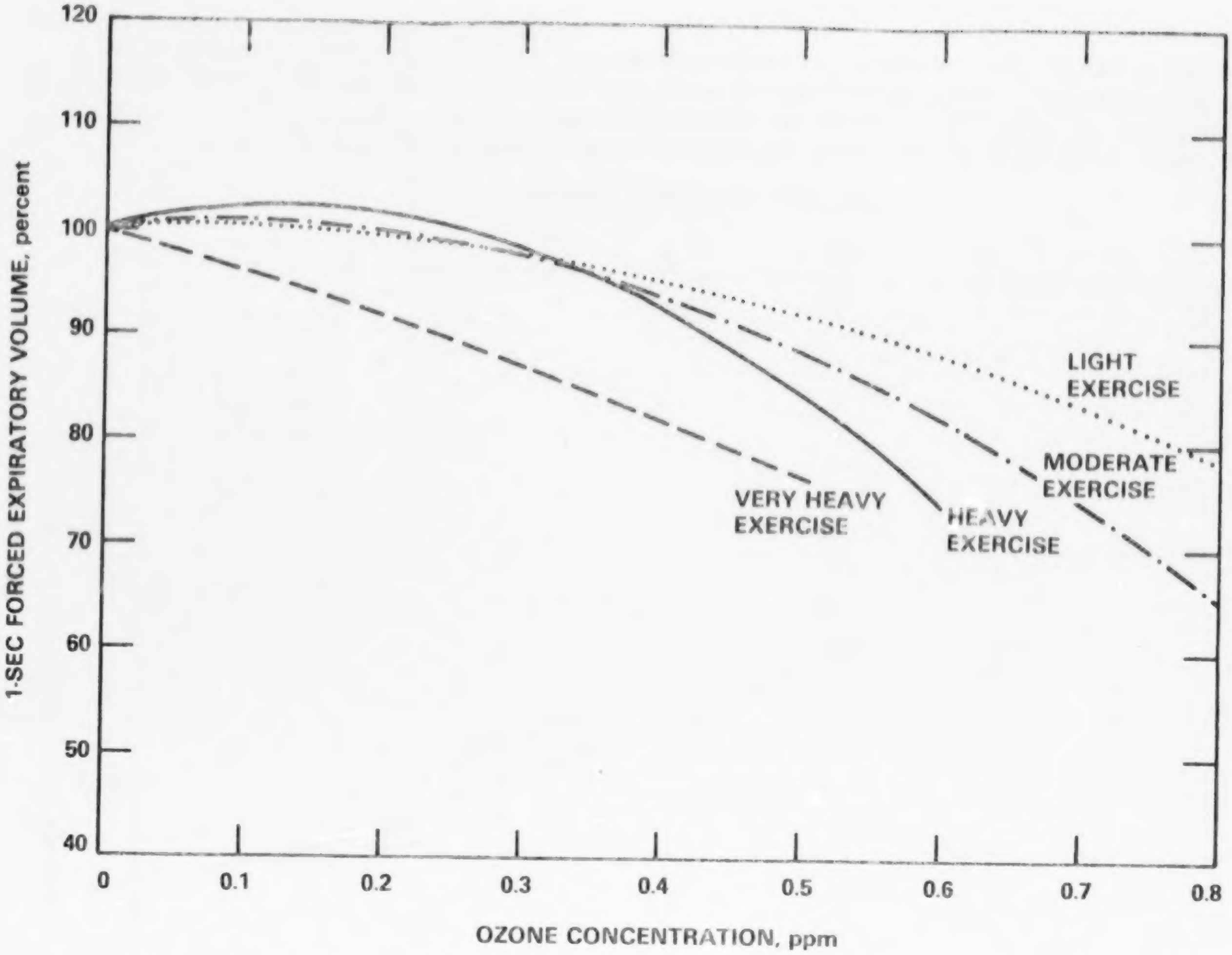

Figure 13-6. Group mean decrements in 1-sec forced expiratory volume during 2-hr ozone exposures with different levels of intermittent exercise: light ($V_E \leqslant 25$ L/min); moderate (V_E =26-43 L/min); heavy (V_E = 44-63 L/min); and very heavy ($V_E \geqslant 64$ L/min). Concentration-response curves are taken from Figures 13-2 through 13-5.

(Table 13-3). In order to compile as complete a data base as possible, complementary data were obtained from published technical reports and from conference proceedings. The original articles often reported data that were either incomplete or that were presented only in graphical form. Only those studies that reported or for which it was possible to calculate, from additional sources, all five critical variables (minute ventilation, O_3 concentration, exposure duration (90 to 150 min), cohort size, and at least FEV_1) were included in the data base. Calibration methods for ozone measurements differed among the studies from which these data were obtained, but the curve parameters proved insensitive to corrections for biases between methods. Thus, the O_3 concentrations as reported in the original articles were used. To minimize inhomogeneity of data, studies that did not utilize the intermittent exercise protocol were not included in the calculations.

Despite methodological and protocol differences among various studies, it was possible to group the reported averaged data by workloads into four categories of exercise: light ($\dot{V}_E \leq 25$ L/min), moderate ($\dot{V}_E = 26$ to 43 L/min), heavy ($\dot{V}_E = 44$ to 63 L/min), and very heavy ($\dot{V}_E \geq 64$ L/min). Subsequent curve-fitting by means of a quadratic regression equation, weighted by sample size, produced clearly differentiated response curves (Figures 13-2 through 13-5) with high correlation coefficients ($r = 0.85$ to 0.97). The 95 percent confidence limits for any of the curves did not exceed +5 percent of response. At 0.6 ppm O_3, the expected average decrement in FEV_1 of lightly exercising subjects is 12 percent (Figure 13-2), while heavy exercise under comparable conditions may lower the FEV_1 by 27 percent (Figure 13-4). Other pulmonary function variables analyzed in the same manner, although not illustrated here, showed the same trend as the FEV_1; but as expected, changes differed in magnitude. For example, the decrements in FVC were smaller, while decrements in FEF_{25-75} were greater, for a given O_3 concentration, than decrements in FEV_1. The Raw shows a similar concentration-dependent, positively correlated response ($r = 0.540$).

A comparison of the respective combinations of minute ventilation ($\dot{V}_E$) and ozone concentration that induce the same amount of functional change, e.g., a 10 percent decrease in FEV_1, further illustrates the interdependence of these two determinants. From the curves in Figure 13-6 it can be seen that very heavy exercise at 0.24 ppm, heavy exercise at 0.43 ppm, moderate exercise at 0.48 ppm, or light exercise at 0.56 ppm O_3 can all be expected to reduce

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME

Ozone[a] concentration, μg/m³	Ozone[a] concentration, ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$, %[d]	Reference[a]
LIGHT EXERCISE							
1470	0.75	MAST, NBKI	90	10	22.5	84.6 ± 1.8	(2) Bates and Hazucha, 1973
1470	0.75		90	10	22.5	81.6 ± 2.2	
1470	0.75		120	10	22.5	79.3 ± 2.7	
1470	0.75		120	10	22.5	76.6 ± 2.7	
1470	0.75	CHEM, NBKI	120	11	20.0	77.2 ± 4.4	(3) Folinsbee et al., 1977b
0	0.0	CHEM, NBKI	120	10	11.2	99.0 ± 15.1	(4) Folinsbee et al., 1978
196	0.1		120	10	11.2	98.4 ± 15.7	
588	0.3		120	10	9.6	99.0 ± 16.1	
980	0.5		120	10	11.8	92.6 ± 17.1	
0	0.00	UV, UV	125	21	22.6	100.3 ± 0.8	(6) Gliner et al., 1983
392	0.20		125	21	22.6	96.9 ± 1.3	
823	0.46[e]		125	21	22.6	81.6 ± 2.7	
0	0.0	CHEM, GPT	120	15	10.0	99.4 ± 5.0	(7) Haak et al., 1984
784	0.4		120	15	10.0	100.0 ± 5.3	
490	0.25	CHEM, NBKI	120	6	20.0	100.3	(8) Hackney et al., 1975c
725	0.37		120	5	20.0	97.7	
980	0.50		120	7	20.0	95.3	
784	0.4	CHEM, NBKI	135	6	20.0	99.5	(9) Hackney et al., 1976
784	0.4		135	9	20.0	95.5	
0	0.00	MAST, NBKI	120	6	22.0	101.4 ± 1.7	(11) Hazucha et al., 1973
0	0.00		120	6	22.0	100.5 ± 3.3	
725	0.37		120	6	22.0	92.6 ± 2.3	
725	0.37		120	6	22.0	96.1 ± 0.7	
1470	0.75		120	6	22.0	73.3 ± 6.8	
1470	0.75		120	6	22.0	72.4 ± 4.7	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration		Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
μg/m³	ppm						
431	0.22	MAST, NBKI	120	4	22.5	101.5	(12) Hazucha et al., 1977
451	0.23		120	4	22.5	93.7 ± 1.4	
470	0.24		120	4	22.5	96.0 ± 3.1	
784	0.40		120	4	22.5	93.9 ± 2.5	
784	0.40		120	4	22.5	91.9 ± 5.9	
784	0.40		120	4	22.5	89.5	
1215	0.62		120	4	22.5	88.0	
1235	0.63		120	4	22.5	86.0	
0	0.00	CHEM, NBKI	120	8	8.4	101.0	(14) Horvath et al., 1979
0	0.00		120	7	8.4	102.3	
490	0.25		120	8	8.2	101.6	
490	0.25		120	7	8.2	98.3	
980	0.50		120	8	7.8	96.9	
980	0.50		120	7	7.8	91.4	
1470	0.75		120	8	7.7	89.2	
1470	0.75		120	7	7.7	81.0	
0	0.0	UV, NBKI	140	12	20.0	101.2	(17) Linn et al., 1979
0	0.0		140	12	20.0	99.8	
392	0.2		140	12	20.0	101.5	
392	0.2		140	12	20.0	99.5	
784	0.40		120	5	11.0	101.7 ± 2.8	(20) Silverman et al., 1976
941	0.48		120	5	11.0	101.4 ± 8.3	
1509	0.77		120	5	11.0	90.4 ± 4.0	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration		Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
$\mu g/m^3$	ppm						
MODERATE EXERCISE							
0	0.00	MAST, NBKI	120	3	25.0	104.9	(1) Bates et al., 1972
1470	0.75		120	3	25.0	69.7	
0	0.0	CHEM, NBKI	100	8	36.0	96.5 ± 4.3	(3) Folinsbee et al., 1977b
0	0.0		100	6	35.0	98.7 ± 6.6	
0	0.0		118	8	36.0	99.4 ± 2.7	
0	0.0		118	6	35.0	96.4 ± 5.5	
0	0.0		125	8	36.0	98.6 ± 6.5	
0	0.0		125	6	35.0	100.7 ± 5.5	
980	0.5		100	8	33.3	89.9 ± 5.9	
980	0.5		100	6	39.2	81.1 ± 6.8	
980	0.5		118	8	33.3	87.8 ± 6.4	
980	0.5		118	6	39.2	81.9 ± 5.6	
980	0.5		125	8	33.3	92.0 ± 6.6	
980	0.5		125	6	39.2	92.3 ± 5.8	
0	0.0	CHEM, NBKI	120	10	32.6	99.4 ± 13.1	(4) Folinsbee et al., 1978
196	0.1		120	10	32.3	101.9 ± 13.8	
588	0.3		120	10	31.0	95.4 ± 16.0	
980	0.5		120	10	32.1	87.3 ± 16.6	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
0	0.00	CHEM, NBKI	135	10	32.0	99.2 ± 4.9	(5) Folinsbee et al , 1980
0	0.00		135	10	32.0	99.7 ± 4.5	
0	0.00		135	10	32.0	101.3 ± 4.4	
0	0.00		135	10	32.0	101.1 ± 4.4	
0	0.00		135	10	32.0	99.6 ± 4.3	
0	0.00		135	10	32.0	100.7 ± 4.8	
0	0.00		135	10	30.0	101.0 ± 4.9	
0	0.00		135	10	30.0	100.3 ± 4.5	
0	0.00		135	10	30.0	99.8 ± 4.7	
0	0.00		135	10	30.0	100.6 ± 4.7	
0	0.00		135	10	31.0	101.4 ± 4.5	
0	0.00		135	10	31.0	101.9 ± 5.1	
0	0.00		135	10	31.0	101.9 ± 5.3	
0	0.00		135	10	31.0	100.9 ± 5.4	
0	0.00		135	10	31.0	100.2 ± 5.1	
392	0.20		135	10	31.0	101.8 ± 4.8	
392	0.20		135	10	31.0	102.5 ± 4.8	
392	0.20		135	10	31.0	102.8 ± 4.7	
392	0.20		135	10	31.0	102.2 ± 4.8	
392	0.20		135	10	31.0	101.3 ± 4.8	
666	0.34		135	10	32.0	101.3 ± 4.6	
666	0.34		135	10	32.0	100.6 ± 4.3	
666	0.34		135	10	32.0	99.7 ± 4.6	
666	0.34		135	10	32.0	96.9 ± 4.8	
666	0.34		135	10	32.0	95.5 ± 4.3	
902	0.46		135	10	30.0	99.8 ± 5.1	
902	0.46		135	10	30.0	95.0 ± 4.8	
902	0.46		135	10	30.0	93.3 ± 6.0	
902	0.46		135	10	30.0	87.0 ± 6.0	
902	0.46		135	10	30.0	91.3 ± 5.0	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration		Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	FEV$_{1\cdot0}$,[d] %	Reference[a]
μg/m³	ppm						
0	0.0	CHEM, GPT	120	29	35.0	101.5 ± 2.6	(7) Haak et al., 1984
0	0.0		120	15	35.0	99.7 ± 4.3	
784	0.4		120	15	35.0	96.9 ± 5.5	
725	0.37	CHEM, NBKI	120	4	25.0	91.7 ± 27.4	(10) Hackney et al., 1977b
725	0.37		120	4	25.0	99.7 ± 18.1	
0	0.0	CHEM, NBKI	120	14	35.0	97.9 ± 5.1	(13) Hazucha, 1981
0	0.0		120	14	35.0	96.0 ± 6.7	
1176	0.6		120	14	35.0	78.8 ± 6.1	
1176	0.6		120	14	35.0	73.1 ± 6.5	
0	0.00	UV, UV	125	24	30.0	99.7 ± 1.0	(15) Horvath et al., 1981
1058	0.54		125	24	30.0	78.9 ± 3.0	
0	0.00	UV, NBKI	120	11	30.0	100.8	(18) Linn et al., 1982
921	0.47		120	11	30.0	88.7	
921	0.47		120	11	30.0	91.4	
921	0.47		120	11	30.0	84.8	
921	0.47		120	11	30.0	87.4	
921	0.47		120	11	30.0	86.6	
921	0.47		120	11	30.0	86.5	
784	0.40	MAST, NBKI	120	5	27.5	94.6 ± 3.5	(20) Silverman et al., 1976
941	0.48		120	5	27.5	95.1 ± 1.9	
1509	0.77		120	5	27.5	79.8 ± 6.4	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	FEV$_{1.0}$,[d] %	Reference[a]
HEAVY EXERCISE							
0	0.0	CHEM, NBKI	120	10	50.4	100.8 ± 16.3	(4) Folinsbee et al., 1978
196	0.1		120	10	49.8	100.5 ± 16.2	
588	0.3		120	10	56.3	93.7 ± 17.5	
980	0.5		120	10	51.4	85.8 ± 19.5	
0	0.0	CHEM, GPT	120	15	57.0	98.7 ± 4.1	(7) Haak et al., 1984
0	0.0		120	15	57.0	101.9 ± 4.3	
784	0.4		120	15	57.0	90.6 ± 4.9	
784	0.4		120	15	57.0	95.6 ± 5.4	
0	0.0	CHEM, NBKI	120	20	45.0	102.5	(16) Ketcham et al., 1977
1176	0.6		120	20	45.0	71.6	
784	0.40	MAST, NBKI	90	5	46.5	96.0	(20) Silverman et al., 1976
784	0.40		120	5	46.5	94.3	
941	0.48		90	5	44.7	89.3	
941	0.48		120	5	44.7	84.4	
0	0.0	CHEM, NBKI	120	10	55.3	98.8 ± 5.6	(21) Stacy et al., 1983
784	0.4		120	12	55.3	92.3 ± 4.8	

TABLE 13-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME (continued)

Ozone[a] concentration		Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
µg/m³	ppm						
VERY HEAVY EXERCISE							
0	0.0	CHEM, NBKI	120	10	66.8	99.7 ± 13.7	(4) Folinsbee et al., 1978
196	0.1		120	10	71.2	97.4 ± 17.6	
588	0.3		120	10	68.4	92.3 ± 12.7	
980	0.5		120	10	67.3	76.1 ± 11.9	
0	0.00	CHEM, UV	150	22	66.2	98.9 ± 2.4	(19) McDonnell et al., 1983
235	0.12		150	22	68.0	95.7 ± 3.2	
353	0.18		150	20	64.6	93.6 ± 3.4	
470	0.24		150	21	64.9	85.6 ± 3.4	
588	0.30		150	21	65.4	83.2 ± 3.8	
784	0.40		150	29	64.3	83.0 ± 3.7	

[a] References are listed alphabetically within each exercise category; reference number refers to data points on Figures 13-2 through 13-5.

[b] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[c] Calibration method: NBKI = neutral buffered potassium iodide; GPT = gas phase titration; UV = ultraviolet photometry.

[d] Data reported as mean ± standard error of the mean; not all references provided standard errors.

[e] Subjects exposed to 0.42 and 0.50 ppm ozone were treated as the same subject group (Gliner et al., 1983).

FEV_1 by 10 percent, on the average. The curves also indicate that there is no threshold concentration; i.e., the concentration below which no measurable effects are induced as assessed by a mean response. Furthermore, the 95 percent confidence limits show that even very low O_3 concentrations (<0.2 ppm) will induce some functional decrements. For example, as Figure 13-4 shows, one may be 95 percent confident that very heavy exercise during exposure to 0.2 ppm ozone will decrease FEV_1 by 5 to 12 percent; and during exposure to 0.1 ppm, by 1 to 7 percent, on the average. Thus, at any ozone concentration there will presumably be healthy individuals who will show effects of the exposure.

Exercise not only stresses the respiratory system but other physiological systems, as well, particularly the cardiovascular and musculoskeletal systems. Various compensatory mechanisms activated within these systems during physical activity might facilitate, suppress, or otherwise modify the magnitude and persistence of the reaction to ozone. Unfortunately, to date only a few of the studies were specifically designed to examine nonpulmonary effects of exercise in ozone atmospheres (Gliner et al., 1979). In one study, very heavy exercise ($\dot{V}_E$ > 64 L/min) at a high ozone concentration (0.75 ppm) reduced post-exposure maximal exercise capacity by limiting maximal oxygen consumption (Folinsbee et al., 1977a); submaximal oxygen consumption changes were inconsistent (Folinsbee et al., 1975). The extent of ventilatory (V_T, f_R) and respiratory metabolic changes ($\dot{V}O_2$) observed during or following the exposure appears to have been related to the magnitude of pulmonary function impairment. Whether such (metabolic) changes are consequent to respiratory discomfort or are the result of changes in lung mechanics or both is still unclear and needs to be elucidated.

13.3.2.3 Environmental Stresses. Environmental conditions such as heat and relative humidity (rh) may enhance subjective symptoms and physiological impairment following O_3 exposure. A hot (31 to 40°C) and/or humid (85 percent rh) environment, combined with exercise in the O_3 atmosphere, has been shown to reduce forced expiratory volume more than similar exposures at normal room temperature and humidity (25°C, 50 percent rh) (Folinsbee et al., 1977b; Gibbons and Adams, 1984). Modification of the effects of O_3 by heat or humidity stress may be attributed to increased ventilation which, like exercise, increases the overall volume of inhaled pollutant and promotes greater penetration into the peripheral areas of the lung.

13.3.3 Other Factors Affecting Pulmonary Response to Ozone

13.3.3.1 Age. Although changes in growth and development of the lung with age have been postulated as one of many factors capable of modifying responsiveness to O_3, studies have not been designed to test adequately for effects of O_3 in different age groups. An enhanced responsiveness of the young to ozone exposure has been suggested from field and epidemiology studies in which decreases in lung function were reported at O_3 concentrations of 0.08 to 0.15 ppm (Kagawa and Toyoma, 1975; Kagawa et al., 1976; Kagawa, 1983; Lebowitz et al., 1982, 1983; Lebowitz, 1984). Symptoms have also been observed in children exposed to 0.10 ppm oxidant and above (Okawada et al, 1979; Makino and Mizoguchi, 1975). No comparable data are available, however, from controlled human studies, since possible age differences in response to O_3 have not been explored systematically in controlled studies.

The influence of age on responsiveness to ozone is also difficult to assess from animal studies. Very few age comparisons have been made within a single study. Raub et al. (1983), Barry (1983), and Barry et al. (1983) studied pulmonary function and morphometry of the proximal alveolar region in neonatal (1-day-old) and adult (6-week-old) rats exposed to 0.08, 0.12, or 0.25 ppm ozone for 12 hr/day, 7 days/week for 6 weeks. A few different responses were observed in the neonates and adults, but they were not major. Generally, neonates and adults were about equally responsive.

The stage of development at initiation of exposure may be an important determinant of age responsiveness. A rat is generally considered to be adult (e.g., sexually mature) at about 60 days of age, while alveolarization of the lungs is complete at roughly 40 days of age. Stephens et al. (1978) exposed rats of various ages (1 to 40 days old) to 0.85 ppm ozone continuously for 1, 2, or 3 days. Rats exposed prior to weaning (20 days old) had few or no effects on lung structure. For rats older than 20 days, centriacinar lesions increased progressively, reached a plateau at 35 days of age, and persisted. Biochemical studies (antioxidant metabolism and oxygen consumption in the lung) of similar design have been conducted by Lunan et al. (1977), Tyson et al. (1982), and Elsayed et al. (1982). In the first two studies, animals were exposed to 0.9 ppm ozone for 96 hr; in the latter study, subjects were exposed to 0.8 ppm ozone for 92 hr. Generally, in rats exposed prior to weaning (about 20 days old), activities of enzymes decreased; in those around weaning age there was no change; and in more mature young rats (35 to 90 days old), enzyme activities increased. Numerous other studies of adult rats using similar methods show increases in these activities. Lunan et al. (1977) observed a peak in the response at 35 days of age, similar to that of Stephens et al. (1978). In the studies of Elsayed et al. (1982), the 7- and 12-day-old rats had 60 percent mortality; the older rats had no mortality. Lunan et al. (1977) used an additional exposure regimen in which rats aged 10, 15, 25, and 32 days were exposed up to 32 to 34 days of age. Thus, the animals had different lengths of exposure. Effects were observed only in the animals 25 and 32 days old. The greatest magnitude of the effect was observed at 32 days of age, regardless of the absolute length of exposure.

Interpretation of these animal studies may be confounded by the exposure techniques used. In some studies, neonates and mothers were exposed together and the possibility exists that the ozone concentration was different in the breathing zone of the neonates. In the Raub et al. (1983) and Barry et al. (1983) studies, this potentially confounding factor was minimized. In other studies, neonates were exposed without mothers. It is not known whether their breathing parameters may have been influenced from the consequent stress. Even without these factors, the dosimetry of ozone in the different age groups is unknown. From the reported studies it appears that rats about 35 days of age respond equivalently to adult animals when exposed to ozone. Responsiveness of rats prior to weaning (about 20 days old) is confounded.

13.3.3.2 Sex. Sex differences in responsiveness to ozone have not been adequately studied. A small number of female subjects have been exposed in mixed cohorts in many human controlled studies, but only three reports gave enough information for a limited comparative evaluation (Horvath et al., 1979; Gliner et al., 1983; DeLucia et al., 1983). Lung function of women, as assessed by changes in $FEV_{1.0}$, appears to be affected more than that of men under similar exercise and exposure conditions, but the differences have not been analyzed systematically. Further research is needed to determine whether differences in lung volumes or differences in exercise capacity during exposure may lead to sex differences in responses to O_3.

The majority of animal studies have been conducted with male animals. Generally, when females have been used they have not been compared to males in the same study. This makes comparisons of sex sensitivity to ozone from animal data virtually impossible. The only exception is a study of effects of ozone in increasing pentobarbital-induced sleeping time (Graham et al., 1981).

Since waking from pentobarbital anesthesia is brought about by xenobiotic metabolism in the liver, this effect is considered to be extrapulmonary. Both sexes of mice, rats, and hamsters were exposed to 1 ppm ozone for 5 hr. Increased sleeping time was observed in all females, but not in male mice or male rats. Male hamsters were affected, but significantly less than the females. The reasons for this sex difference are unknown. Rats have major sex differences in xenobiotic metabolism, but the other species do not.

13.3.3.3 Smoking Status. Differences between smokers and nonsmokers have been studied often, but the data are not documented well and are often confusing. Published results indicate a discrepancy in findings. Hazucha et al. (1973) and Bates and Hazucha (1973) appear to have demonstrated greater responses (FVC, MMFR) in nonsmokers at 0.37 ppm O_3, but the responses were reversed at 0.75 ppm (RV, FEV_1, $\dot{V}_{max50}$, and MMFR). Kerr et al. (1975) observed greater responses (FRC, SG_{aw}, R_L, FEV, and symptoms) in nonsmokers at 0.5 ppm O_3 for 6 hr. DeLucia et al. (1983) observed similar results for VC, FEV_1, MMFR, f_B, and V_T at 0.3 ppm O_3 (1 hr, CE). Kagawa and Tsuru (1979a) stated that the effects of ozone among nonsmokers were greater for the 0.5 than for the 0.3 ppm O_3 exposure levels (2 hr); a later study (Kagawa, 1983) showed that nonsmokers had a greater response (SG_{aw}) to 0.15 ppm (2 hr, IE). Shephard et al. (1983) found a slower and smaller change in spirometric variables in smokers at 0.5 and 0.75 ppm (2 hr, IE). None of these controlled studies have examined the effects of different amounts of smoking. Epidemiological studies have detected an increase of symptoms (cough, nose, and eye irritation) in heavy smokers compared to others at 0.08 ppm O_3 and above (Zagraniski et al., 1979). The general trend, however, is to imply that smokers are less sensitive than nonsmokers.

13.3.3.4 Nutritional Status. Posin et al. (1979) found that human volunteers receiving 800 (about 4 times the recommended daily units) or 1,600 (a very high supplement) IU vitamin E for 9 weeks as a supplement showed no differences in blood biochemistry from unsupplemented volunteers when exposed to 0.5 ppm ozone for 2 hours. The biochemical parameters studied included red cell fragility, hematocrit, hemoglobin, glutathione concentration, acetylcholinesterase, glucose-6-phosphate dehydrogenase, and lactic acid dehydrogenase activities. Hamburger and Goldstein (1979) studied the agglutination of rat red cells by the lectin concanavalin A after *in vivo* exposure to 0.5 to 2 ppm ozone for 2 hours or incubation *in vitro* with 1 ppm ozone for 2 hours. Agglutination was decreased by ozone exposure, but the number of concanavalin A binding sites on red cells was not decreased. Hamburger et al. (1979) also studied the effects of ozone exposure on the agglutination of human erythrocytes by concanavalin A. As with rat erythrocytes, pre-incubation with malonaldehyde, an oxidation product of polyunsaturated fatty acids, decreased concanavalin A agglutination of red cells exposed _in vitro_ to ozone. Red cells obtained from 29 subjects receiving 800 IU vitamin E (a high supplement) or a placebo were exposed to 0.5 ppm ozone for 2 hours. Following ozone exposure, a slight decrease in agglutination occurred in cells from subjects who did not receive vitamin E supplementation, but the results were not statistically significant.

Increased activity of the glutathione peroxidase system may be one of the most sensitive indices of exposure to $\leq$ 1 ppm of O_3 measured biochemically because it is involved in antioxidant metabolism. Increases in the glutathione peroxidase system have been reported after exposure of rats on a vitamin E-deficient diet to levels as low as 0.1 ppm O_3 for 7 days (Chow et al., 1981; Mustafa, 1975; Mustafa and Lee, 1976). The dietary vitamin E fed to the rats influenced the ozone-induced increase of this system. For example, when the diet of rats had 66 ppm of vitamin E, increased glutathione peroxidase activity was observed at 0.2 ppm of O_3; with 11 ppm of vitamin E, increases occurred at 0.1 ppm (Mustafa and Lee, 1976). Several other investigators have shown that vitamin E deficiency in rats makes them more susceptible to these ozone-induced enzymatic changes (Chow et al., 1981; Plopper et al., 1979; Chow and Tappel, 1972).

Morphological studies of ozone-exposed vitamin E-deficient or supplemented rats have been undertaken to correlate the biochemical findings with morphological alterations (Plopper et al., 1979; Chow et al., 1981; Schwartz et al., 1976; Sato et al., 1976, 1978, 1980). Scanning and transmission electron microscopy were clearly shown to be better than light microscopy for visualization of the ozone lesions. Lesions were worse in vitamin E-deficient or marginally supplemented rats than in highly supplemented rats, supporting the finding from mortality (Donovan et al., 1977) and biochemical studies that vitamin E is protective. Despite the presence of vitamin E in the diets of these animals, the morphological lesion resulting from ozone exposure was unchanged. Vitamin E thus alters the rate and extent of toxicity, but not the lesion itself.

The difference in response between animals and man with regard to the protective effects of vitamin E against ozone toxicity may lie in the pharmacokinetics of vitamin E distribution in the body. Redistribution of vitamin E from extrapulmonary stores to the lung is slow. Short exposures to ozone may not allow adequate time for redistribution and for a protective effect to be observed. Animal exposures in which the striking effects of vitamin E on ozone toxicity were observed were generally conducted over long times. Human subjects were exposed for shorter times and lower concentrations because of ethical considerations. Thus, the protective effects of vitamin E might likewise be demonstrated in man, but might require longer times and higher ozone exposures. In addition, animal studies are generally conducted with a deficient diet (0 ppm vitamin E) group for comparison. The respective human group would very likely not have had a substantial deficiency. Thus, the antioxidant properties of vitamin E in preventing ozone-initiated peroxidation *in vitro* are well demonstrated and the protective effects *in vivo* are clearly demonstrated in rats and mice. No evidence indicates, however, that man would benefit from increased vitamin E intake relative to ambient ozone exposures. Further, vitamin E protection is not absolute and can be overcome by continued ozone exposure. The vitamin E effects do support the general idea, however, that lipid peroxidation is involved in ozone intoxication.

13.3.3.5 *Red Blood Cell Enzyme Deficiencies*. The enzyme glucose-6-phosphate dehydrogenase (G-6-PD) is essential for the function of the glutathione peroxidase system in the red blood cell (RBC), the enzyme system proposed as having an integral part in the decomposition of fatty acid peroxides or hydrogen peroxide formed by O_3-initiated polyunsaturated fatty acid peroxidation (see Section 13.5.1). Therefore, Calabrese et al. (1977) has postulated that individuals with a hereditary deficiency of G-6-PD may be at-risk to significant hematological effects from O_3 exposure. However, there have been too few studies performed to reliably document this possibility. Most ozone studies have been with red blood cells from rodents, even though differences may exist between rodent and human RBCs. Calabrese and Moore (1980) and Moore et al. (1981) have pointed out the lack of ascorbic acid synthesis and the relatively low level of glucose-6-phosphate dehydrogenase (G-6-PD) in man compared to active ascorbic acid synthesis and high levels of G-6-PD in mice and rats. Although this species comparison is based on a very limited data base, the authors point out the importance of developing animal models that can accurately predict the response of G-6-PD-deficient humans to oxidant stressor agents such as O_3. This group has suggested the use of the C57L/J strain of mice and the Dorset sheep as better animal models for hematological studies since these species have levels of G-6-PD closer to those in man, especially those levels found in G-6-PD-deficient patients. The RBCs of Dorset sheep, however, appear to be no more sensitive to ozone than normal human RBCs even though the G-6-PD levels are very low. Further *in vitro* studies (Calabrese et al., 1982, 1983; Williams et al., 1983a,b,c) have demonstrated that the responses of sheep and normal human erythrocytes were very similar when separately incubated with potentially toxic O_3 intermediates, but that G-6-PD-deficient human erythrocytes were considerably more susceptible. Even if O_3 or a reactive product of O_3-tissue interaction were to penetrate the RBC after *in vivo* exposure, it is unlikely that decrements in reduced glutathione levels leading to chronic hemolytic anemia would be of functional significance for the affected individual. More research may therefore be needed to determine the susceptibility of these individuals to O_3-induced hemolysis from near-ambient O_3 exposures.

13.3.4 Effects of Repeated Exposure to Ozone

13.3.4.1 Introduction. Ozone toxicity may be mitigated through altered responses that are functional, biochemical, or morphological in type. For example, in response to O_3 there may be an increase in tissue or cellular levels of antioxidants, which act to quench free radicals and reduce lipid peroxidation. At present the underlying mechanisms for this response are unclear and the effectiveness of such mitigating forces in protecting the long-term health of the individual against O_3 is still uncertain (Bromberg and Hazucha, 1982).

Reduction of responses associated with repeated exposure to O_3 is generally referred to as "adaptation." Earlier work in animals that focused primarily on reductions in pulmonary edema and mortality rate to assess this process employed the term "tolerance" (Chapter 10, Section 10.3.5). Other terms, including "tachyphylaxis," have also been used to describe this phenomenon. The distinction, if any, among these terms with respect to O_3 and its effects has never been established in a clear, consistent manner.

13.3.4.2 Development of Altered Responsiveness to Ozone. Successive daily brief exposures to O_3 ($<$ 0.7 ppm for $\sim$ 2 hrs) induce a typical temporal pattern of response (Chapter 11, Section 11.3). Maximum functional changes that occur after the first exposure day (airway resistance, bronchial reactivity tests)

(Farrell et al., 1979; Dimeo et al., 1981) or the second exposure day (spirometric tests) become progressively attenuated on each of the subsequent days (Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982). By the fourth day of exposure, the effects are, on the average, not different from those observed following control (air) exposure. Individuals need between 3 and 7 days to develop full attenuation, with more sensitive subjects requiring more time (Horvath et al., 1981; Haak et al., 1984). The magnitude of a peak response appears to be directly related to O_3 concentration (Folinsbee et al., 1980; Haak et al., 1984). Whether varying the length or the frequency of exposure will modify the time course of this altered responsiveness has not been explored. Full attenuation, even in ozone-sensitive subjects, does not persist for more than 3 to 7 days in most individuals (Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982), while partial attenuation might persist for up to 2 weeks (Horvath et al., 1981). Although symptomatic response is generally related to the magnitude of the functional response, partial symptomatic attenuation appears to persist longer, for up to 4 weeks (Linn et al., 1982). Ozone concentrations inducing only minimal functional effects (< 0.2 ppm) have not elicited altered responsiveness to O_3 in either pulmonary function or airway responsiveness (Folinsbee et al., 1980; Dimeo et al., 1981). The last findings are consistent with the proposition that functional attenuation may not occur in the airways of individuals living in communities where the ambient ozone levels do not exceed 0.2 ppm. The difficulty, however, of drawing such inferences on the basis of narrowly defined laboratory studies is that under ambient conditions a number of uncontrollable factors will modify the response. Most notably, other pollutants may interact with ozone to modify changes in the host at lower concentrations during generally more protracted exposures. The evidence suggesting that Los Angeles residents exhibit functional attenuation of the response to O_3 is sparse and requires confirmation (Hackney et al., 1976, 1977a,b; Linn et al., 1983).

13.3.4.3 Mechanisms of Altered Responsiveness to Ozone. The time course, type, and consistency of changes of such indices as symptoms, lung volumes, flows, resistances, and bronchial reactivity strongly implicate vagal sensory receptors (cholinergic post-ganglionic pathways) in substantially modifying the development of altered responsiveness to O_3 (Dimeo et al., 1981). Post-exposure inhalation of atropine (a bronchodilator) blocked completely, though only transiently, the increase in bronchial reactivity (Golden et al., 1978;

Holtzman et al., 1979). Similarly, inhalation of isoproterenol (a bronchodilator) relieved all symptoms and normalized functional changes induced by ozone (Golden et al., 1978). Since afferent vagal activity is one of the principal modifiers of bronchomotor tone, any attenuated changes will be reflected in airway smooth muscle response and thus in altered airway resistance, which is used as a convenient index of bronchoconstriction. Besides the vagal component, numerous other mechanisms might play an important role in the development of altered responsiveness to O_3; e.g., release of mediators (Linn et al., 1982) or increased airway mucosa permeability (Davis et al., 1980). The relative importance and the overall contribution of any of these mechanisms is still unclear.

Whether laboratory animals develop functional attenuation of responses similar to that observed in human subjects, as measured by airway resistance or forced expiratory flow rates, is unreported. In this regard, recent experiments by Gertner et al. (1983a,b,c) are noteworthy, since they offer some clues on possible mechanisms. They demonstrated that even a brief exposure of the peripheral airways of dogs to ozone triggered functional response that appeared to be mediated through both reflex and humoral pathways. The reflex-mediated response was subject to attenuation after repeated exposure, whereas the response mediated humorally was not.

As noted previously, functional and symptomatic attenuation of responses to O_3 in human subjects is typically preceded by a limited period during which effects are slightly exaggerated. The latter period corresponds roughly in time to the period of heightened responsiveness to a provocative aerosol, response also caused by O_3 (Dimeo et al., 1981). Recent experimental evidence in laboratory animals points to an intimate relationship between the cellular response to O_3-induced injury, as measured by the appearance of neutrophils in the airway epithelium of dogs exposed to O_3, and airway hyperresponsiveness, as determined with a provocative aerosol (Holtzman et al., 1983a,b; Fabbri et al., 1984; Sielczak et al., 1983). When mobilization of the neutrophils was prevented by prior treatment with hydroxyurea (O'Byrne et al., 1983), or the neutrophilic infiltration found after ozone exposure was depressed (Fabbri et al., 1983), no increase was seen in airway responsiveness.

Since many proposed mechanisms of altered responsiveness to O_3 in humans are difficult if not impossible to investigate, animal studies become essential in providing necessary confirmatory evidence. Numerous basic metabolic processes in humans and animals appear to be very similar (Mustafa and Tierney, 1978;

Boushey et al., 1980). Some mechanisms underlying these processes at the cellular and subcellular level studied extensively in animals do provide some clues on possible mechanisms in humans. It has been shown that human and animal leukocytes, pulmonary macrophages, and neutrophils produce superoxide radicals not only as a product of a vital biological reduction of molecular oxygen but also as a result of stressful stimuli (Pick and Kersari, 1981). Excessive production of radicals without adequate scavenging will injure the supporting tissues, while the attenuation of response to successive stimuli suppresses the release of free oxygen radicals and depresses the chemotactic responsiveness of the cells (Mustafa and Tierney, 1978; Bhatnagar et al., 1983). Accumulation of inflammatory cells at the site of injury and subsequent release of proteases capable of degrading connective tissue may upset the protease-antiprotease balance critical for controlling the extent of inflammation and injury. Reported ozone inactivation of human α_1-proteinase inhibitor (Johnson, 1980) observed *in vitro* and perturbation of lung collagen metabolism seen *in vivo* in animals (Hussain et al., 1976; Mustafa and Tierney, 1978) could be factors potentially affecting inflammatory response. Furthermore, the metabolic attenuation of propyl hydroxylase (a key enzyme in collagen synthesis) activity (Hussain et al., 1976a,b), and concurrent changes in superoxide dismutase activity, which catalyzes the dismutation of the superoxide free radical (Bhatnagar et al., 1983), could be another important pathway to the development of altered responsiveness to O_3. The glutathione peroxidase system, which provides another line of defense by protecting cells from lipid peroxides, also exhibits metabolic attenuation (Chow, 1976; Chow et al., 1976).

With time, there is a reduction in intensity and a change in composition of the inflammatory response. Partial remission occurs with continuous or intermittent exposure. There are no data showing how important the timing and duration of the O_3 pulsations may be in influencing the induction and remission of the inflammatory reaction. The latter issue has potential significance for public health, since exposure to ambient air pollution at levels of concern is essentially intermittent. The timing and intensity of exposure within the community, and consequently its potential for inducing altered responses, are likely to be highly variable. Differences within the population in patterns of activity and biological status may be expected to contribute to this variability.

13.3.4.4 Conclusions Relative to Attenuation with Repeated Exposures. Insofar as different effects of O_3 share the same mechanism(s), they may be expected to follow approximately similar time courses in their development of altered responsiveness to O_3. As a corollary, effects that are not linked mechanistically should follow independent although not necessarily dissimilar time courses, assuming that they are involved in this process.

The attenuation of acute effects of O_3 after repeated exposure, such as changes in respiratory mechanical behavior, have been well documented in controlled exposure studies. In contrast, there is no practical means at present of assessing the role of altered responsiveness to O_3 in human populations chronically exposed to ozone. There have been no epidemiological studies designed to test whether the modification of changes involving irritative symptoms, pulmonary function, or morbidity occur in association with photochemical air pollution. It might be added that the proposition would be difficult to test epidemiologically. Thus, scientists, as well as regulators, must rely mainly on inferences and extrapolations from animal experimentation.

Altered responsiveness to O_3 may be viewed as a process exhibiting concentration/response characteristics. Concentrations of O_3 that have no detectable effect appear not to invoke changes in response to subsequent exposures at higher O_3 concentrations. Insofar as this generalization is valid, it suggests that photochemical air pollution may induce altered responses only in individuals who previously responded to exposure. Over some higher range (0.4 to 0.8 ppm) of exposure, changes occurring after repeated exposure may be optimal so that recovery (assessed by pulmonary function tests) after initial damage is virtually complete. Above this optimal range, persistent or progressive damage is most likely to accompany protracted exposure. The attenuation, however, of pulmonary function (and the time course of attenuation) following repeated exposure to O_3 does not necessarily follow the morphological or biochemical pattern of responses.

Responses to O_3, whether functional, biochemical, or morphological, have the potential for altering responses during repeated or continuous exposure. There is an interplay between tissue inflammation, hyperresponsiveness, ensuing injury (damage), and changes in response. The hyperresponsiveness followed by attenuation of responses caused by O_3 may be viewed as obverse or sequential states in a continuing process.

13.3.5 Relationship Between Acute and Chronic Ozone Effects

Understanding the relationship between acute effects that follow O_3 exposure of man or animals and the effects that follow long-term exposures of man or animals is crucial to the evaluation of possible human health effects of oxidant pollutants. Most of the acute responses to O_3 described in animals and man tend to return to control (filtered air) values with time after the exposure ends. While effects of longer periods of exposure have been documented in laboratory animals (Chapter 10), long-term exposures of human beings have not been done because of possible health hazards. In fact, little is known about the long-term implications of acute damage or about the chronic effects of prolonged exposure to O_3 in man.

With newer techniques, pulmonary functions of experimental animals can be more completely evaluated and correlated with biochemical and morphological parameters. Long-term exposure of rats to less than 1.0 ppm O_3 results in increased lung volume, especially at high transpulmonary pressures (Bartlett et al., 1974; Moore and Schwartz, 1981; Raub et al., 1983; Costa et al., 1983). Costa et al. (1983) also observed increased pulmonary resistance and, at low lung volumes, decreased maximum expiratory flows in rats exposed to 0.2 or 0.8 ppm O_3 6 hr/day, 5 days/week for 62 exposures. The latter change was related to decreased airway stiffness or to narrowing of the airway lumen. Raub et al. (1983), in neonatal rats exposed to 0.12 or 0.25 ppm O_3 12 hr/day for 42 days, observed significantly lower peak inspiratory flows during spontaneous respiration, in addition to the increased lung volumes noted above. While Yokoyama and Ichikawa (1974) did not find changes in lung static pressure-volume curves of rats exposed to 0.45 ppm O_3 6 hr/day, 6 days/week for 6 to 7 weeks, Martin et al. (1983) reported increased maximum extensibility of alveolar walls and increased fixed lung volumes following exposure of rabbits to 0.4 ppm O_3 7 hr/day, 5 days/week for 6 weeks.

Wegner (1982) studied pulmonary functions in bonnet monkeys exposed to 0.64 ppm O_3 8 hr/day, 7 days/week for up to 1 year. After 6 months of exposure, significant increases in pulmonary resistance and in the frequency dependence of pulmonary compliance were reported. In the monkeys exposed 1 year, Wegner (1982) reported significantly increased pulmonary resistance and inertance and decreased flows during forced expiratory maneuvers at low lung volumes and decreased volume expired in 1 second (FEV_1). These findings were interpreted as indicating narrowing of the peripheral airways. Following a 3-month postexposure period, static lung compliance tended to decrease in both exposed and control monkeys, but the decrease in exposed monkeys was significantly greater than that for control monkeys. Although values for other parameters studied in control and exposed monkeys were not significantly different at the end of the postexposure period, they tended to be substantially different. Wegner (1982) interpreted these differences as an indication that recovery was not complete following the 3-month postexposure period. This interpretation appears reasonable, as fewer monkeys were available for pulmonary function testing at the end of the postexposure period because monkeys were terminated for biochemical and morphological evaluation at the end of each experimental period. To find the same level of statistical significance with fewer animals, the difference of the means would have to be greater at the end of the postexposure period than at the end of the exposure.

Morphological alterations in both rats and monkeys tend to decrease with increasing duration of exposure to O_3, but significant alterations in the centriacinar region have been reported at the end of long-term exposures of rats (Boorman et al., 1980; Moore and Schwartz, 1981; Barry et al., 1983), monkeys (Eustis et al., 1981), and dogs (Freeman et al., 1973). While repair, as indicated by DNA synthesis by repair cells, starts as early as 18 hours of exposure (Castleman et al., 1980; Evans et al., 1976a,b,c; Lum et al., 1978), damage continues throughout long-term exposures, but at a lower rate.

Morphological damage reported in the centriacinar region of rats and monkeys exposed to less than 1.0 ppm O_3 for 42 to 90 days includes damage to ciliated and alveolar type 1 cells; hyperplasia of nonciliated bronchiolar and alveolar type 2 cells, with extension of nonciliated bronchiolar cells into more distal structures than in unexposed controls; accumulation of intraluminal inflammatory cells; and in rats, but not reported in monkeys, thickening of interalveolar septa (Boorman et al., 1980; Moore and Schwartz, 1981; Eustis et al., 1981; Barry et al., 1983). Freeman et al. (1973) exposed dogs to 1.0 to 3.0 ppm O_3 8 to 24 hr/day for 18 months. Dogs exposed to 1.0 ppm O_3 8 hr/day had the mildest changes, including minimal fibrosis of terminal airways and adjacent alveoli with a few "extra" macrophages in these areas. Epithelial hyperplasia and metaplasia and increased fibrosis were seen in dogs exposed to higher concentrations or more hours per day. These investigators also observed that bronchiolar walls were thickened by both epithelial hyperplasia and intramural fibrosis, which reduced the caliber of small airways. Lungs from the bonnet monkeys studied by Wegner (1982) were evaluated morphologically and morphometrically by Fujinaka (1984). At the end of the 1-year exposure to

0.64 ppm O_3 for 8 hr/day, a significant increase was found in the total volume of respiratory bronchioles in the lung, but their lumens were smaller in diameter because of thickened epithelium and other wall components. The reduction in diameter of the first generation respiratory bronchioles correlates with the results of the pulmonary function tests performed by Wegner (1982). Cuboidal bronchiolar epithelial cells in respiratory bronchioles were hyperplastic. Walls of respiratory bronchioles contained significantly more macrophages, lymphocytes, plasma cells, and neutrophils. Neither the numbers of fibroblasts nor amount of stainable collagen was increased significantly, but there was more amorphous intercellular material. There was also a significant increase in arteriolar media and intima.

Lung collagen content was increased after short-term exposure to less than 1.0 ppm O_3 (Last et al., 1979; Last et al., 1981). This change continued during long-term exposure (Last and Greenberg, 1980; Last et al., 1984). Exposure to less than 1.0 ppm O_3 resulted in increased lung collagen content in both weanling and adult rats exposed for 6 and 13 weeks, respectively, and in young monkeys exposed for 1 year (Last et al., 1984). Some of the weanling rats and their controls were examined after a 6-week postexposure period following the 6-week O_3 exposure during which all rats breathed filtered air. During this postexposure period, the differences in lung collagen content between exposed and pair fed controls increased rather than decreased. Thus, with respect to this biochemical alteration, the postexposure period was one of continued damage rather than recovery.

A similar observation of continued damage during a postexposure period was reported by Gillespie (1980) in pulmonary function studies of beagle dogs exposed for 5 years to a variety of pollutants (see Chapter 10, Section 5.2). Similar pulmonary function tests were performed during and at the end of the 5-year exposure in a Cincinnati, Ohio, laboratory and repeated in a Davis, California, laboratory after a 2-year postexposure period. The postexposure values of the control group were similar to values at the end of the exposure and to values for other healthy beagle dogs at Davis. All exposed groups had more functional abnormalities at the end of the 2-year postexposure period than at the end of the exposure. Thus, the postexposure period was one of continued damage, as evaluated by pulmonary function tests.

Continuation of the centriacinar inflammatory process during long-term O_3 exposures is especially important, as it appears to be correlated with remodeling of the centriacinar airways (Boorman et al., 1980; Moore and Schwartz, 1981; Fujinaka, 1984). There is morphometric (Fujinaka, 1984), morphologic (Freeman et al., 1973), and functional evidence (Costa et al., 1983; Wegner, 1982) of distal airway narrowing. Continuation of the inflammation also appears to be correlated with increased lung collagen content (Boorman et al., 1980; Last et al., 1979; Last et al., 1984).

The distal airway and arteriolar changes described in the above studies of ozone-exposed animals have many similarities to those reported in lungs from cigarette smokers (Niewoehner et al., 1974; Cosio et al., 1980; Hale et al., 1980; Wright et al., 1983). Even though cigarette smoking has been linked with emphysema in humans, however, there is no evidence of emphysema in the lungs of animals exposed to O_3. The previous criteria document for O_3 (U.S. Environmental Protection Agency, 1978) cited three studies reporting emphysema in laboratory animals after exposure to <1 ppm O_3 for prolonged periods (P'an et al., 1972; Freeman et al., 1974; Stephens et al., 1976); but a reevaluation of these findings based on the currently accepted definition of emphysema does not find any evidence for such claims (see Chapter 10; Section 3.1.4.2). Since then, no similar exposures (i.e., same species, O_3 concentration, and times) have been documented to confirm observations of emphysematous changes in the lungs of animals exposed to O_3.

13.3.6 Resistance to Infection

Normally the mammalian respiratory system is protected from bacterial and viral infections by the integrated activity of the mucociliary, phagocytic, and immunological defense systems. Animal models and isolated cells have been used to assess the effects of oxidants on the various components of these pulmonary defenses and to measure the ability of these systems to function as an integrated unit in suppressing pulmonary disease. In these studies, short-term (3 hr) exposure to O_3 at concentrations of 0.08 to 0.10 ppm can increase the incidence of mortality from lower respiratory bacterial infection (Coffin et al., 1968; Ehrlich et al., 1977; Miller et al., 1978). Subchronic exposure to 0.1 ppm caused similar effects (Aranyi et al., 1983). Following short-term exposures to O_3, a number of alterations in vital defenses have been shown, such as (1) impairment in the ability of the lung to inactivate bacteria and viruses (Coffin et al., 1968; Coffin and Gardner, 1972; Goldstein et al., 1974, 1977; Ibrahim et al., 1976; Nakajima et al., 1972; Ehrlich et al., 1979); (2) reduced effectiveness of mucociliary clearance (Phalen et al., 1980; Frager et al., 1979; Kenoyer et al., 1981; Abraham et al., 1980); (3) immunosuppression (Campbell and Hilsenroth, 1976; Thomas et al., 1981b); (4) a significant reduction in number of pulmonary defense cells (Coffin et al., 1968; Alpert et al., 1971); and (5) macrophages with less phagocytic activity, less mobility, more fragility and membrane alterations, and reduced lysosomal enzymatic activity (Dowell et al., 1970; Hurst et al., 1970; Hurst and Coffin, 1971; Goldstein et al., 1971, 1974, 1977; Hadley et al., 1977; Ehrlich et al., 1979; McAllen et al., 1981; Witz et al., 1983; Amoruso et al., 1981). Such effects have been reported in a variety of species of animals following either short-term and subchronic exposure to O_3 alone or in combination with other airborne chemicals (Gardner et al., 1977; Aranyi et al., 1983; Ehrlich, 1980, 1983; Grose et al., 1980, 1982; Phalen et al., 1980; Goldstein et al., 1974). Studies have also indicated that the activity level of the test subject is an important variable that can influence the determination of the lowest effective concentration of the pollutant (Illing et al., 1980).

The major problem remaining is the assessment of the relevance of these animal data to humans. If animal models are to be used to reflect the toxicological response occurring in humans, then the end point for comparison of such studies should not be mortality, since today few individuals die of bacterial pneumonias. A better comparison in humans would be the increased prevalence of respiratory illness in the community. Such a comparison is proper since both mortality (animals) and morbidity (humans) result from a loss in pulmonary defenses. Ideally, studies of pulmonary host defenses should be performed in man using epidemiological or volunteer methods of study. Unfortunately, such studies have not yet been reported. Therefore, attention must be paid to experiments conducted with animals.

Our present knowledge of the physiology, metabolism, and function of host defense systems has come primarily from various animal systems, but it is generally accepted that the basic mechanisms of action of these defense cells and systems are similar in both animals and man. The effects seen in animals represent alterations in basic biological systems. One would not expect to see an equivalent response (e.g., mortality) in man, but one could assume that similar alterations in basic defense mechanisms could occur in humans, who possess equivalent pulmonary defense systems. It is understood, however, that different exposure levels may be required to produce similar responses in humans. The concentrations of O_3 at which effects become evident can be influenced by a number of factors, such as preexisting disease, dietary factors, combinations with other pollutants, and/or the presence of other environmental stresses. Thus, one could hypothesize that humans exposed to O_3 could experience decrements in host defenses, but at the present time one cannot predict the exact concentration at which effects may occur in man or the severity of the effect.

13.3.7 Extrapulmonary Effects of Ozone

Because of the reactivity of O_3 with biological tissue, it was not intuitively obvious that O_3 would ever reach the circulation. Several studies discussed in Chapters 10 and 11 are indicative, however, of either direct or indirect extrapulmonary effects of ozone exposure. For example, alterations in red blood cell morphology, deformity, and enzymatic activity, as well as chromosomal effects in circulating lymphocytes, have been reported in man and laboratory animals. Other organ systems of the body may also be involved. Exposure to high concentrations of O_3 may have central nervous system effects, since decrements in performance of exercise and vigilance tasks have been observed in man and laboratory animals. Cardiovascular, reproductive, and teratological effects of O_3 have also been reported in laboratory animals, along with changes in endocrine function; but the implications of these findings for human health are difficult to judge at the present time. More recent studies in laboratory animals have shown that hepatic metabolism of xenobiotic compounds may be impaired by O_3 inhalation. While some systemic effects, such as those associated with exercise performance, may be secondary to pulmonary damage, the others are more difficult to conceptualize. These effects may result from direct contact with O_3 or from contact with a reactive product of O_3 that penetrates to the blood and is transported to the other organs.

Chromosomal and mutational effects of ozone are controversial. In cells in culture, a significant increase in the frequency of sister chromatid exchanges has been reported to occur after exposure to concentrations of ozone as low as 0.25 ppm for 1 hr (Guerrero et al., 1979). Lymphocytes isolated from animals were found to have significant increases in the numbers of chromosomal (Zelac et al., 1971a,b) and chromatid (Tice et al., 1978) aberrations, after 4- to 5-hr exposures to 0.2 and 0.43 ppm ozone ozone, respectively. Single-strand breaks in DNA of mouse peritoneal exudate cells were measurable after a 24-hr exposure to 1 ppm ozone (Chaney, 1981). Gooch et al. (1976)

analyzed the bone marrow samples from Chinese hamsters exposed to 0.23 ppm of O_3 for 5 hr and the leukocytes and spermatocytes from mice exposed for up to 2 weeks to 0.21 ppm of O_3. No effect was found on either the frequency of chromatid or chromosome aberrations, nor were there any reciprocal translocations in the primary spermatocytes. An increase (although not significant) was observed in chromatid lesions in peripheral blood lymphocytes from 6 human subjects exposed to 0.5 ppm ozone for 6 or 10 hr (Merz et al., 1975). Subsequent investigations, however, with more human subjects exposed to ozone at various concentrations and for various times have failed to show any cytogenetic effect considered to be the result of ozone exposure (McKenzie et al., 1977; McKenzie, 1982; Guerrero et al., 1979). In addition, epidemiological studies have not shown any evidence of chromosome changes in peripheral lymphocytes of humans exposed to the ambient environment (Scott and Burkart, 1978; Magie et al., 1982). Clearly, additional evaluation of the human mutagenic potential of ozone is needed. Evidence now available, however, fails to demonstrate any mutagenic effect of ozone in humans when exposure schedules are used that are representative of exposures that the population at large might actually experience.

With the exception of peripheral blood lymphocytes, the genotoxic effects of ozone for all of the other body tissues is unknown. It is somewhat puzzling that in spite of the experimental difficulties that may be encountered no cytogenetic investigations have been conducted in the respiratory tissues of animals exposed to ozone. These tissues are exposed to the highest concentrations and are also the target of most of the toxic manifestations of ozone. Clearly, one cannot extrapolate ozone-induced genotoxicity data from peripheral blood lymphocytes to other organs, such as the lungs.

Ozone exposure produces a number of hematological and serum chemistry changes both in rodents and man, but the physiological significance of these studies is unknown. Most of the hematological changes appear linked to a decrease in RBC GSH content (Menzel et al., 1975; Buckley et al., 1975; Posin et al., 1979; Linn et al., 1978) at concentrations of 0.2 ppm for 30 to 60 min in man, or 0.5 ppm for 2.75 hr in sheep, or 0.5 ppm continuously for 5 days in mice and rats. Heinz bodies, disulfide cross-linked methemoglobin complexes attached to the inner RBC membrane, were detected in mice exposed to ozone (Menzel et al., 1975). Inhibition of RBC acetylcholinesterase was found in mouse (Goldstein et al., 1968), human (Buckley et al., 1975), and squirrel monkey RBCs (Clark et al., 1978) at concentrations of 0.4 to 0.75 ppm and times as short as 2.75 hr in man or 4 hr/day for 4 days in monkeys. Loss of RBC acetylcholinesterase could either be mediated by membrane peroxidation or by loss of acetylcholinesterase thiol groups at the active site. Dorsey et al. (1983) observed that the deformability of CD-1 mouse RBCs decreased on exposure to 0.7 and 1 ppm for 4 hr. Deformability also decreased at 0.3 ppm, but was not statistically significant. These data also support the concept of membrane damage to circulating RBCs. While it is theoretically possible that species differences in ozone sensitivity may exist because of differences in G-6-PD (see Section 13.3.3.5), most experiments have reported a close similarity in the responses of animal and normal human RBCs to ozone exposure.

13.4 HEALTH EFFECTS IN POTENTIALLY SUSCEPTIBLE INDIVIDUALS

13.4.1 Patients with Chronic Obstructive Lung Disease (COLD)

Patients with mild COLD have not shown increased sensitivity to O_3 in controlled human exposure studies, and the epidemiological findings are inconsistent. Linn et al. (1982, 1983) and Hackney et al. (1983) showed no changes in symptoms or function at 0.12, 0.18, or 0.25 ppm O_3 (1 hr, IE). Likewise, Solic et al. (1982) and Kehrl et al. (1983) found no significant changes in symptoms or function at 0.2 or 0.3 ppm O_3 (2 hr, IE). At higher concentrations, however, Kulle et al. (1984) found decreased function in a group of 20 smoking chronic bronchitics at 0.4 ppm (3 hr, IE) on day 1 of exposure and upon reexposure at day 6. In an epidemiological study, Balchum (1973) found aggravation of symptoms and decreased function in COLD patients at an oxidant concentration of 0.11 ppm.

There is suggestive evidence that bronchial reactivity is increased in some subjects with COLD (two of three) following exposure to 0.1 ppm O_3 (König et al., 1980), and that arterial O_2 saturation is reduced slightly in these subjects during exposure to 0.12 ppm O_3 combined with exercise (Linn et al., 1982; Hackney et al., 1983). The latter observation is consistent with the occurrence of unequally distributed defects in mechanical function in the lung.

One difficulty in attempting to characterize the responsiveness of patients with COLD is that they may exhibit a wide diversity of clinical and functional states. These range from a history of smoking, cough, and minimal functional defects to chronic disability that is usually combined with severe defects in blood gases or respiratory mechanical behavior. The chief locus of damage may also vary: either the bronchi (chronic bronchitis) or parenchyma (emphysema) may dominate the clinical picture. Finally, the mixture of acute and chronic inflammatory processes may vary considerably among patients. There has been no attempt to sort out these manifestations of COLD in the design of these studies.

13.4.2 Asthmatics

There is yet no laboratory evidence that mild asthmatics are functionally more sensitive than healthy individuals to O_3. Linn et al. (1978) found no significant changes in lung function, as indicated by forced expiratory spirometry or the nitrogen washout test, when asthmatic subjects with mild to moderate bronchial obstruction were exposed to 0.20 ppm O_3 for 2 hr with intermittent light exercise; increased symptom scores were noted, however. Silverman (1979) found minimal changes in forced expiratory spirometry following 2-hr exposures of asthmatic subjects to 0.25 ppm O_3 while at rest. Although group mean changes were not statistically significant, one third of the subjects who rested for 2 hr while inhaling 0.25 ppm O_3 demonstrated a greater than 10 percent decrement in lung function, and it is doubtful if this would have been true for normal subjects. Finally, in ambient air exposures containing 0.17 ppm O_3, Linn et al. (1980) found small but statistically significant decrements in forced expiratory measures in both normal and asthmatic subjects, following 2-hr exposures with intermittent light exercise. The magnitude of functional responses in both groups was practically the same.

The studies reported above are not considered definitive since major limitations leave open the question of whether the pulmonary function of asthmatics is more affected by O_3 than that of normals. Intake of medication was not controlled in several of the studies, and some subjects continued to use oral medication when being tested. Some of the subjects in one study (Linn et al., 1978) showed evidence of chronic obstructive lung disease in addition to asthma. Most of the normal subjects in the Linn et al. (1980) study, in which asthmatics were compared to normals, had a history of allergy and appeared atypically reactive to the O_3 exposure. In addition, the subjects in these studies either performed light exercise or rested while exposed. In view of the recognized importance of minute ventilation, which increases proportionately with the intensity of exercise, in determining the response to O_3, additional testing at higher levels of exercise should be undertaken.

Finally, it may be that the specific measurements of pulmonary function and the exposure protocols employed in the above studies were inappropriate for ascertaining pulmonary effects in asthmatic subjects. Asthma is essentially characterized by bronchoconstriction. Compared to airway resistance, some measures of forced expiratory spirometry are less sensitive to bronchoconstriction, since fairly severe bronchoconstriction must occur in order to affect decrements in these measures. McDonnell et al. (1983), reporting on normal subjects exposed to levels of O_3 as low as 0.12 ppm with heavy intermittent exercise, attributed small decrements in forced expiratory spirometry and increased symptoms to a reduced inspiratory capacity resulting from stimulation or sensitization of airway receptors by O_3. They also observed that there was no correlation between changes in airway resistance and forced expiratory spirometry for individual subjects, which prompted them to postulate two different mechanisms of action. It may be that the sensitivity of the mechanism affecting inspiratory capacity is the same in asthmatics and normals, while the mechanism affecting airway resistance is different.

Epidemiological findings stand somewhat in contrast to clinical findings in that they provide some evidence of exacerbation of asthma at ambient concentrations of O_3 below those generally associated with symptoms or functional changes in healthy adults. For example, Zagraniski et al. (1979) reported an increased prevalence of symptoms among clinic asthmatic patients in association with a mean ambient O_3 concentration of 0.08 ppm; Whittemore and Korn (1980) reported an increasing risk of asthmatic attack with increasing ambient oxidant concentrations between 0.04 and 0.15 ppm; and Lebowitz et al. (1982, 1983) found similar results when O_3 concentrations were above 0.056 ppm (there was an interaction between O_3 and ambient temperature). Lebowitz (1984) also reported finding a reduction in expiratory peak flow rate in asthmatics at O_3 concentrations above 0.056 ppm. The inconsistency of the epidemiological findings and the controlled human exposure studies with bronchoconstriction could be the result of several factors: (1) insensitivity of the pulmonary function tests employed, (2) insufficient clinical information in these studies; or (3) interactions of the pollutants inducing responses in the epidemiological studies.

13.4.3 Subjects with Allergy, Atopy, and Hyperreactive Airways

These diagnostic categories have generally been established through history-taking in clinical exposures and through skin-testing and other diagnostic procedures in epidemiological studies. The information available on the responsiveness of these individuals, i.e., whether they differ from normal non-allergic, non-atopic individuals, is sparse.

Hackney et al. (1977a) found decreases in spirometric function among atopic individuals exposed to 0.5 ppm O_3 at rest. Neither Folinsbee et al. (1978), in a controlled laboratory exposure, nor Linn et al. (1980), in a field study in the Los Angeles area, distinguished between the responses of normal subjects and allergic non-asthmatic subjects. In the latter study, spirometric function was reduced and symptoms were increased in association with an average ambient O_3 concentration of 0.12 ppm. As with asthmatics (see 13.4.2.2), Zagraniski et al. (1979) found that non-asthmatic allergic subjects experienced an increased prevalence of symptoms in association with ambient O_3 concentrations above 0.08 ppm: cough and hay fever were exacerbated. Similarly, Lebowitz et al. (1982, 1983) also reported an increase in eye symptoms among non-asthmatic allergic subjects in association with O_3 concentrations above 0.056 ppm. The association was independent of other air pollutants and weather.

Some normal subjects with no prior history of respiratory symptoms or allergy demonstrate increased nonspecific airway sensitivity resulting from O_3 exposure (Golden et al., 1978; Holtzman et al., 1979; König et al., 1980; Dimeo et al., 1981; Kulle et al., 1982b). Airway responsiveness is typically defined by changes in specific airway resistance produced by a provocative bronchial challenge to drugs like acetylcholine, methacholine, or histamine, administered after O_3 exposure. In one study (Holtzman et al., 1979), in which subjects were classified as atopic or nonatopic based on medical history and allergen skin testing, the induction and time course of increased bronchial reactivity after exposure to O_3 were unrelated to the presence of atopy. An association of O_3-induced increases in airway responsiveness with airway inflammation has been reported in dogs at high O_3 concentrations (1 to 3 ppm) (Holtzman et al., 1983a,b; Fabbri et al., 1984); and in sheep at 0.5 ppm O_3 (Sielczak et al., 1983). Little is known, however, about this relationship in animals at lower O_3 concentrations (<0.5 ppm), and the possible association between O_3-induced inflammation and airway hyperresponsiveness in human subjects has not been explored systematically.

13.5 EXTRAPOLATION OF EFFECTS OBSERVED IN ANIMALS TO HUMAN POPULATIONS

13.5.1 Species Comparisons

Comparisons of the effects of ozone on different animal species is of interest in attempting to understand whether man might experience similar effects. For example, if only one of several tested species experienced a given effect of ozone, this effect might be species specific and not occur in man. Conversely, if several animal species, with all their inherent differences, shared a given effect of ozone, it is likely that some element present in all mammalian species, including man, was susceptible to ozone. A commonality of effects across species would be expected, provided the effect was related to a mechanism which is shared across species. In the case of ozone, the proposed major molecular mechanisms of action are the oxidation of polyunsaturated fatty acids and the oxidation of thiols or amino acids in tissue proteins or small-molecular-weight peptides. Thus, if the affected molecules are identical across all species, then any differences in the observed responses between species would be a function of species differences in delivered doses or of subsequent processes of toxicity. For example, a likely target site for O_3 toxicity is the cellular membrane, particularly the membrane of cells like the Type 1 and ciliated cell which cover a large surface area of the respiratory tract. Since there are no major interspecies differences in cell membranes and membranes are composed of proteins and lipids, then both proposed molecular mechanisms of O_3 toxicity could occur at the cellular membrane. In fact, the two proposed hypotheses most likely occur simultaneously. The consequent toxic impact on the membrane, the cell, and surrounding tissue would be influenced by species differences in antioxidant defenses or repair mechanisms. Some of the products of ozone oxidation are water-soluble and can diffuse from the site of oxidation in the membrane into cytosol or the circulation. The extrapulmonary effects of ozone exposure may be due to such circulating products. Inflammatory cells appear in the lung after ozone exposure. Peroxides are active in the inflammatory process as intermediates in the prostaglandin and leukotriene cascades. Some of the peroxides formed from ozonized arachidonic acid are active as prostaglandin agonists, but apparently can not be converted to more complex prostanoids, at least by human platelets. Fatty acid ozonides could release histamine and cause both local and pulmonary edema. Many of these substances (histamine, prostaglandins, etc.) will not only enter additional metabolic reactions, but will also act as local or, if distributed by the pulmonary circulation, as systemic mediators. Depending on the target site and the amount released, they may be vasoactive, modulate bronchomotor tone, stimulate receptors, or trigger reflex reactions and thus influence lung or other organ function. Such functional changes might be transient or become more permanent if tissue structure was altered as well. The extent of interdependence among biochemical, morphological, immunological, and functional changes induced by O_3 remains to be determined. Since current knowledge is not sufficiently advanced to assess such events quantitatively, only qualitative hypotheses can be made, based on the available evidence. A commonly accepted hypothesis is that if ozone causes an effect in several animal species, it can cause a similar effect in man. It is important to note that this is a qualitative probability; it does not permit assessment of the concentrations at which man might experience the common effect.

The health data base for ozone consists of hundreds of studies with about 7 species, and even more strains, of animals. Generally, for a given effect, whether it be on lung morphology, physiology, biochemistry, or host defenses, all species tested were responsive to ozone, albeit sometimes at different concentrations. The few studies of several species having at least two points of identity for comparison will be discussed.

Morphological examinations of the lungs of several mammalian species have been conducted after ozone exposure. Of the groups studied, there are significant differences in lung structure. Man, nonhuman primates, and dogs have both nonrespiratory and respiratory bronchioles, while respiratory bronchioles are either absent or poorly developed in mice, rats, and guinea pigs. Additional differences exist. Nonetheless, a characteristic ozone lesion occurs at the junction of the conducting airways and the gaseous exchange tissues, whatever the species specifics of the structure are. The typical effect in all the species examined is damage to ciliated and Type 1 cells and hyperplasia of nonciliated bronchiolar cells and Type 2 cells. An increase in inflammatory cells is also observed. Such changes were observed after a 7-day intermittent exposure of monkeys to 0.2 ppm (Dungworth et al., 1975; Castleman et al., 1977) and of rats to 0.2 ppm (Schwartz et al., 1976). With different exposure regimens, similar effects occur in cats (0.26 ppm, endotracheal tube, about 6 hr, Boatman et al., 1974), mice (0.5 ppm, 35 days, Zitnik et al., 1978), and guinea pigs (0.5 ppm, 6 mo, Cavender et al., 1978). For these studies, lower concentrations of ozone were not tested. Unfortunately, quantitative comparisons between monkey and rat studies is not possible because of inadequate data. Nonetheless, a rough equivalency of responses was observed under similar exposure conditions between species having major structural differences. Since the monkey lung may be the most representative model of the human lung, the possibility is enhanced that man would experience similar effects.

Pulmonary function of eight species of animals has been studied after exposure to ozone. Short-term exposure for 2 hr to O_3 concentrations as low as 0.22 ppm produces rapid, shallow breathing. Similar changes in respiration have been observed in man during comparable ozone exposure, as shown in Table 13-7. The onset of these effects is rapid and appears to be related to the ozone concentration. In a recent review, Mauderly (1984) compared changes in breathing patterns of humans and guinea pigs during and after a 2-hr exposure to 0.7 ppm O_3. The respiratory frequency decreased and tidal volume increased with similar patterns during exposure and returned toward normal in the first 3 hr after exposure.

Enhanced airway reactivity to inhaled bronchoconstrictive agents has also been observed in animals and man after O_3 exposure (Table 13-8). Short-term exposure to O_3 concentrations as low as 0.32 ppm increases airway resistance following inhalation of the drugs acetylcholine, carbachol, methacholine, or histamine in sheep, dogs, and humans. However, the time course of this response differs. A maximum response is obtained immediately after exposure in man but appears to be delayed by 24 hr in sheep and dogs.

Mauderly (1984) has also compared the effect of 2-hr O_3 exposures on airway constriction in humans, guinea pigs, and cats. Although measured indices of airflow limitation are similarly depressed in both animals and man, there are too many differences in the experimental methods and too few species studied to provide an adequate comparison.

Qualitative comparisons of changes in breathing patterns and airway reactivity indicate that many similarities occur during exposure of animals and humans to ozone. However, quantitative extrapolation of these effects may be limited by the small number of studies having similar experimental procedures and similar exposure levels. Other effects of short- and long-term ozone exposure on lung function have been observed (Chapter 10) but there are insufficient points of identity in the experiments to permit direct comparisons among animal species or between animals and man.

TABLE 13-4. COMPARISON OF THE ACUTE EFFECTS OF OZONE ON BREATHING PATTERNS IN ANIMALS AND MAN

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b] method	Exposure duration	Activity[c] level (V_E)	Observed effects(s)	Species	Reference
392 686	0.20 0.35	UV	1 hr (mouthpiece)	CE(77.5)	Increased f_R and decreased V_T.	Human	Adams and Schelegle, 1983
431 804 1568	0.22 0.41 0.8	CHEM	2 hr	R	Concentration-dependent increase in f_R for all exposure levels.	Guinea pig	Amdur et al., 1978
470 588 784	0.24 0.30 0.40	CHEM	2.5 hr	IE(65)	Increased f_R and decreased V_T.	Human	McDonnell et al., 1983
588	0.3	MAST	1 hr (mouthpiece)	CE(34.7, 51)	Increased f_R and decreased V_T.	Human	DeLucia et al., 1983
588	0.3	UV	1 hr (mouthpiece)	CE(66)	Increased f_R and decreased V_T.	Human	DeLucia and Adams, 1977
666 1333 2117 2646	0.34 0.68 1.08 1.35	NBKI	2 hr	R	Increased f_R and decreased V_T during exposure to all O_3 concentrations.	Guinea pig	Murphy et al., 1964
725 980 1470	0.37 0.50 0.75	MAST	2 hr	IE(29)	Dose-dependent increase in f_R and decrease in V_T.	Human	Folinsbee et al., 1975
980	0.5	NBKI	2 hr	R	Increased f_R.	Guinea pig	Yokoyama, 1969
1100	0.56	CHEM	2 hr	R	Abnormal, rapid, shallow breathing while exercising on a treadmill after exposure.	Dog	Lee et al., 1979

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry; NBKI = neutral buffered potassium iodide.

[c] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise; CE = continuous exercise.

TABLE 13-5. COMPARISON OF THE ACUTE EFFECTS OF OZONE ON AIRWAY REACTIVITY IN ANIMALS AND MAN

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b] method	Exposure duration	Activity[c] level (V_E)	Observed effects(s)	Species	Reference
627	0.32	MAST	2 hr	R	SR_{aw} increased with ACh challenge.	Human	König et al., 1980
784	0.4	CHEM	3 hr	IE(4-5xR)	SG_{aw} decreased with methacholine; attenuation develops with repeated exposures.	Human	Kulle et al., 1982b
784	0.4	UV	2 hr	IE(2xR)	SR_{aw} increased with histamine challenge; attenuation develops with repeated exposure. No effect on bronchial reactivity at 0.2 ppm.	Human	Dimeo et al., 1981
980	0.5	CHEM	2 hr	R	R_L increased with carbachol 24 hr but not immediately after exposure.	Sheep	Abraham et al., 1980
1176	0.6	UV	2 hr	IE(2xR)	SR_{aw} increased with histamine and methacholine in atopic and non-atopic subjects.	Human	Holtzman et al., 1979
1176	0.6	CHEM	2 hr	R	Bronchoreactivity to histamine; may persist for up to 3 weeks.	Human	Golden et al., 1978
1372	0.7	CHEM	2 hr	R	R_L increased with histamine 24 hr but not 1 hr after O_3 exposure.	Dog	Lee et al., 1977
1960	1.0	UV	2 hr	R	R_L increased with ACh and histamine 1 hr and 24 hr after exposure.	Dog	Holtzman et al., 1983a,b

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[c] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise.

Species comparisons of host defense against infection are possible for alveolar macrophages. After an intermittent (8 hr/day) 7-day exposure to 0.2 ppm ozone, an increased number of alveolar macrophages was observed in the lungs of both rats and monkeys (Castleman et al., 1977; Dungworth, 1976; Stephens et al., 1976). Although numerous other macrophage studies have been conducted, there are insufficient points of identity for species comparison.

Rats and monkeys have been examined for changes in lung biochemistry following ozone exposure. In these animals exposed for 7 days (8 hr/day) to 0.8 ppm ozone (DeLucia et al., 1975), glucose-6-phosphate dehydrogenase activity was elevated to a roughly equivalent degree. Glutathione reductase activity was increased in rats, but not monkeys. Chow et al. (1975) also compared these species after exposure to 0.5 ppm ozone for 8 hr/day for 7 days. Antioxidant enzymes were increased in the rats, but not the monkeys. The authors referred to "relatively large variations" in the monkey data. Oxygen consumption was measured in rats and monkeys after a 7-day (8 hr/day) exposure to several levels of ozone (Mustafa and Lee, 1976). Rhesus monkeys may have been slightly less responsive than rats. However, at 0.5 ppm ozone, bonnet monkeys and rats had roughly equivalent increases. In all of these reports, there was no mention of statistical comparisons between species or of power calculations that would indicate whether under the experimental conditions of data variability, there was equivalent power to statistically detect effects in both species. In a few of the reports, the number of animals was not given. Mustafa et al. (1982) compared mice to 3 strains of rats exposed to 0.45 ppm ozone continuously for 5 days. Antioxidant metabolism and oxygen consumption were measured. Generally, increases in enzyme activities were observed in both species; in several cases the increase in the mice was statistically greater than the increase in the rats.

For extrapulmonary effects, the only species comparison using identical methods was made by Graham et al. (1981). Female mice, rats, and hamsters had an increase in pentobarbital-induced sleeping time after a 5-hour exposure to 1 ppm ozone. Under the experimental conditions used, relative species responsivity cannot be assessed.

An overview of the animal toxicological data for ozone indicates that rats are the most prevalent species tested. Other species often used include mice, rabbits, guinea pigs, and monkeys. A few dog and hamster studies exist. As has been noted above, very few species comparisons can be made due to differences in exposure regimens and measurement techniques. Even when direct comparisons are possible, interpretation is difficult. Statements regarding responsiveness can be made. Statements about sensitivity (e.g., responses to an equivalent delivered dose) cannot be made until more dosimetry and other types of data are available. Nonetheless, it is remarkable that even with the wide variation in techniques and experimental designs, acute and subchronic exposures to levels of ozone less than 0.5 ppm produce similar types of responses in many species of animals. Thus, it may be hypothesized that man may experience more types of effects than have been established in human clinical studies. Types of effects for which substantial animal data bases exist include changes in lung structure, biochemistry, and host defenses. However, the actual risk to man breathing ambient levels of ozone cannot be determined until the animal data can be quantitatively extrapolated to man.

13.5.2 Dosimetry Modeling

The discussion of species comparisons in response to ozone exposure presented above (Section 13.5.1) assesses the net effects of species differences in sensitivity and dosimetry. An uncoupling of these two elements is required to be able to make quantitative interspecies comparisons of toxicological results from different experiments. In this context, dosimetry refers to determination of the amount of ozone which reaches specific sites in animals and man, while sensitivity relates to the likelihood of equivalency of biological response given that the same dose of ozone is delivered to a target site in different species.

Although additional research is needed on dosimetry and on species sensitivity before quantitative extrapolations of effective O_3 concentrations can be made between species, only dosimetry is sufficiently advanced for discussion here. Because the factors affecting the transport and absorption of O_3 are general to animals and to man, dosimetry models can be formulated that use appropriate species anatomical and ventilatory parameters to describe O_3 absorption. Thus far, theoretical modeling efforts (McJilton et al., 1972; Miller et al., 1978) have focused on the lower respiratory tract.

Largely due to the technical ease of measuring ozone uptake in the head, nasopharyngeal removal of ozone has been experimentally studied in the dog (Vaughan et al., 1969; Yokoyama and Frank, 1972; Moorman et al., 1973), rabbit

(Miller et al., 1979), and guinea pig (Miller et al., 1979). To date, information on nasopharyngeal removal of O_3 in man is not available. Since nasopharyngeal removal of O_3 serves to lessen the insult to lower respiratory tract tissue which is thought to be more sensitive, an assessment of species differences in this area is critical to interspecies comparisons of dosimetry.

Damage to all respiratory tract regions occurs in animals exposed to O_3, with location and intensity dependent upon concentration. When comparisons are made at the analogous anatomical site, the morphological effects of O_3 on the lungs of a number of animal species are remarkably similar. Despite inherent differences in anatomy between various experimental animals and man, the junction between the conducting airways and the gas exchange region is most affected by O_3 exposure in animals (See 10.3.1) and most likely will be the principal site affected in man. Dosimetry model simulations (Miller et al., 1978) predict that the maximal tissue dose occurs at the region of predominant morphological damage in animals. The overall similarity of the predicted O_3 dose patterns in animal lungs studied thus far (rabbits and guinea pigs) extends to the simulation of O_3 uptake in humans (see 10.2.3.1).

The consistency and similarity of the human and animal lower respiratory tract dose curves lend strong support to the feasibility of extrapolating to man the results obtained on animals exposed to O_3. In the past, extrapolations have usually been qualitative in nature. With additional research in areas which are basic to the formulation of dosimetry models, quantitative dosimetric differences among species can be determined. If in addition, more information is obtained on species sensitivity to a given dose, significant advances can be made in quantitatively extrapolating animal toxicological results to man. Since animal studies are the only available approach for investigating the full array of potential disease states induced by exposure to O_3, quantitative use of animal data is in the interest of better establishing O_3 levels to which man can safely be exposed.

13.6 HEALTH EFFECTS OF OTHER PHOTOCHEMICAL OXIDANTS AND POLLUTANT MIXTURES

Ozone is considered to be chiefly responsible for the adverse effects of photochemical air pollutants largely, if not exclusively, because of its relative abundance compared with other photochemical oxidants. Still, the coexistence of other reactive oxidants (Section 13.2.2) suggests that the potential effects of these other oxidants should be examined. Not unexpectedly, however, animal and clinical research has centered largely on O_3; very limited effort has been devoted to studies of peroxyacetyl nitrate (PAN) and hydrogen peroxide (H_2O_2). Field and epidemiological studies evaluate health effects associated with exposure to the ambient environment, making it difficult to single out the oxidant species responsible for the observed effects.

13.6.1 Effects of Peroxyacetyl Nitrate

There have been far too few controlled toxicological studies with the other oxidants to permit any sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. The few animal toxicology studies on PAN indicate that it is much less acutely toxic than O_3. When the effects seen after exposure to O_3 and PAN are examined and compared, it is obvious that the test animals must be exposed to concentrations of PAN much greater than those needed with O_3 to produce a similar effect on lethality, behavior modification, morphology, or significant alterations in host pulmonary defense system (Campbell et al., 1967; Dungworth et al., 1969; Thomas et al., 1979, 1981a).

All of the available controlled human studies with other photochemical oxidants have been limited to a series of reports on the effects of PAN on healthy young and middle-aged males during intermittent exercise on a treadmill (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975). No significant effects were observed at PAN concentrations of 0.25 to 0.27 ppm. Two additional studies at 0.24 ppm (Raven et al., 1976) and 0.30 ppm (Smith, 1965) of PAN suggested a possible limitation on forced expiratory volume and flow, but not enough data are available to evaluate the significance of this effect.

Field and epidemiological studies have found very few specific relationships between reported health effects and PAN concentrations. The increased prevalence of eye irritation reported during ambient air exposures has been associated with PAN as well as other photochemical reaction products (National Air Pollution Control Association, 1970; Altshuller, 1977; National Research Council, 1977; U.S. Environmental Protection Agency, 1978; Okawada et al., 1979). In one of these studies (Okawada et al., 1979), eye irritation was produced experimentally in high school students at concentrations of PAN >0.05 ppm. An increased incidence of other health symptoms such as chest discomfort was reported along with eye irritation as PAN concentrations increased from 0 to 0.012 ppm (Javitz et al., 1983). However, the significance of these symptomatic responses is questionable since functional changes reported in this study for the subjects exposed to total oxidants (O_3 and PAN) were similar to those found for O_3 alone.

13.6.2 Effects of Hydrogen Peroxide

Controlled toxicological studies on H_2O_2 have been performed at concentrations much higher than those found in the ambient air (see Section 13.2), and the majority have been mechanistic studies using various in vitro techniques for exposure. Very limited information is available on the health significance of inhalation exposure to gaseous H_2O_2 in laboratory animals. No significant effects were observed in rats exposed for 7 days to >95 percent H_2O_2 gas with a concentration of 0.5 ppm in the presence of inhalable ammonium sulfate particles (Last et al., 1982). Because H_2O_2 is highly soluble, it is generally assumed that it does not penetrate into the alveolar regions of the lung but is instead deposited on the surface of the upper airways (Last et al., 1982). Unfortunately, there have not been studies designed to look for possible effects in this region of the respiratory tract.

A few in vitro studies have reported cytotoxic, genotoxic, and biochemical effects of H_2O_2 when using isolated cells or organs (Stewart et al., 1981; Bradley et al., 1979; Bradley and Erickson, 1981; Speit et al., 1982; MacRae and Stich, 1979). Although these studies can provide useful data for studying possible mechanisms of action, it is not yet possible to extrapolate these responses to those that might occur in the mammalian system.

13.6.3 Interactions with Other Pollutants

Controlled human exposures have not consistently demonstrated any enhancement of respiratory effects for combined exposures of O_3 with SO_2, NO_2, CO, and H_2SO_4 or other particulate aerosols. Ozone alone is considered to be responsible for the observed effects of those combinations or with multiple mixtures of these pollutants. Studies reviewed in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978) suggested that mixtures of SO_2 and O_3 at a concentration of 0.37 ppm are potentially more active than would be expected from the behavior of the gases acting separately (Bates and Hazucha, 1973; Hazucha and Bates, 1975). High concentrations of inhalable aerosols, particularly H_2SO_4 or ammonium sulfate, could have been responsible for the results (Bell et al., 1977); however, subsequent studies of O_3 mixtures with SO_2, H_2SO_4, or ammonium sulfate have not conclusively demonstrated any interactive effects (Bedi et al., 1979, 1982; Kagawa and Tsuru, 1979c; Kleinman et al., 1981; Kulle et al., 1982a; Stacy et al., 1983).

Combined exposure studies in laboratory animals have produced varied results, depending upon the pollutant combination evaluated and the measured variables. Additive and/or possibly synergistic effects of O_3 exposure in combination with NO_2 have been described for increased susceptibility to bacterial infection (Ehrlich et al., 1977; Ehrlich, 1980, 1983), morphological lesions (Freeman et al., 1974), and increased antioxidant metabolism (Mustafa et al., 1984). Additive effects from combined exposures to O_3 and H_2SO_4 have also been reported for host defense mechanisms (Gardner et al., 1977; Last and Cross, 1978; Grose et al., 1982) but not for morphology (Cavender et al., 1977; Moore and Schwartz, 1981).

Early studies in animals exposed to complex mixtures of UV-irradiated auto exhaust containing oxidant concentrations of 0.2 to 1.0 ppm demonstrated a greater number of effects compared to those reported for nonirradiated exhaust (Chapter 10, Section 5.3). No significant differences were found in the magnitude of the response either with or without the presence of sulfur oxides in the mixture. Although the effects described in these studies would be difficult to associate with any particular oxidant species, they are qualitatively similar to the general effects described for exposure to O_3 alone.

A major limitation of field and epidemiological studies includes the interference or potential interactions between O_3 and other pollutants in the environment. The lack of quantitative measurements of oxidant concentrations has limited the usefulness of these studies. Nevertheless, there is still concern that combinations of oxidant pollutants, including precursors of oxidants, contribute to the decreased function and exacerbation of symptoms reported in asthmatics (Zagraniski et al., 1979; Whittemore and Korn, 1980; Linn et al., 1980, 1983; Lebowitz et al., 1982, 1983; Lebowitz, 1984) and in children and young adults (Kagawa and Toyoma, 1975; Kagawa et al., 1976; Kagawa, 1983; Lebowitz et al., 1982, 1983). Possible interactions between O_3 and total suspended particulate matter have been reported with decreased expiratory flow in children (Lebowitz et al., 1982, 1983; Lebowitz, 1984) and adults with symptoms of airway obstructive disease (Lebowitz et al., 1982, 1983) and with increased symptom rates in asthmatics (Zagraniski et al., 1979).

The effects of interaction between inhaled oxidant gases and other environmental pollutants on the lung have not been systematically studied. In fact, one of the major problems with the available literature on interaction studies is the exposure design. Most of the controlled studies have not used concentrations of combined pollutants that are found in the ambient environment. It may be desirable to place greater research emphasis on characterizing sequential patterns of air pollutant exposure which may have quite different effects compared with continuous exposure to pollutant mixtures. An alternative approach might be to study the interaction of photochemical oxidant species and/or precursors of photochemical oxidants. However, since these issues are complex, they must be addressed experimentally using exposure regimens for combined pollutants that are more representative of ambient ratios of peak concentrations, frequency, duration, and time intervals between events.

13.7 IDENTIFICATION OF POTENTIALLY AT-RISK POPULATIONS OR SUBPOPULATIONS

13.7.1 Introduction

The identification of a population or subpopulation as the group to be protected by a national ambient air quality standard depends upon a number of factors, including (1) the identification of one or more specific biological endpoints (effects) that individuals within a population should be protected from; and (2) the identification of those individuals in whom those specific endpoints are observed (a) at lower concentrations than in other individuals, (b) with greater frequency than in other individuals, (c) with greater consequences than in other individuals, or (d) at various combinations of "effects levels," frequency, or consequences. In addition, as discussed in Chapter 2, other factors such as activity patterns and personal habits, as well as actual and potential exposures to the pollutant in question, must be taken into account when identifying one or more subpopulations potentially at risk from exposure to that pollutant.

In the following sections, biological and other factors that have been found to predispose one or more subpopulations to particular risk from exposure to photochemical oxidants are discussed. It should be noted that these factors are discussed in relation to ozone exposure only. There are too few controlled studies with the other oxidants to permit a sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. The following sections also include estimates of the number of individuals in the United States that fall into certain categories of potentially at-risk subpopulations.

It must be emphasized that the final identification of those effects that are considered "adverse" and the final identification of "at-risk" populations are both the domain of the Administrator.

13.7.2 Potentially At-Risk Individuals

Sensitivity to ozone varies within and among individuals. The factors suspected of altering sensitivity to ozone are numerous. Those actually known to alter sensitivity, however, are few, largely because few have been examined adequately to determine definitively their effects on sensitivity. The discussion below presents information on the factors that are thought to have the potential for affecting sensitivity to ozone, along with what is actually known from the data regarding the importance of these factors. The terms "sensitivity" and "susceptibility" have been used interchangeably in the Clean Air Act and are also used interchangeably in this discussion.

Sensitivity to a specified dose of an air pollutant may be greater or less than normal. Statistical analysis is generally relied upon to establish the range of normal responses for a particular biological endpoint, and to distinguish those responses that are indicative of increased sensitivity and those that are indicative of decreased sensitivity.

Susceptibility may be conferred by some predisposing host factor, such as immunological or biochemical factors; or by some condition, such as preexisting disease. Susceptibility may also result from some aspect of the growth or decline of lung development (e.g., greater bronchomotor tone in childhood, loss of lung function in the elderly), or some previous infectious or immunological process (e.g., childhood respiratory trouble, prior bronchiolitis or other lower respiratory tract infections, and prior asthma). Sensitivity may arise from some prior exposure, that is, one that entails a response, as in "sensitization"; or may result from cross-reactivity to chemicals. Sensitivity may also be simply an unusual response upon exposure, possibly resulting from prior challenge with respiratory irritants).

Most human studies do not perform the complex diagnostic procedures needed to classify study subjects properly, nor do they usually determine the mechanism of response (i.e., underlying immunological, biochemical, or structural character). Furthermore, even diagnostic labels, such as COLD, asthma, allergy, and atopy, are not usually based on sufficient clinical evaluation nor standardized inclusion/exclusion criteria, so that differences in such classifications within and between studies are bound to occur. For example, there are few studies in which bronchoconstrictor challenges, skin or blood antibody testing, or other procedures were performed that characterize disease status, let alone radiographic studies. In epidemiological studies, often not even baseline pulmonary function is determined. Yet, even if these tests are performed, a relatively large group of apparently healthy subjects, not previously identified as being susceptible or sensitive to O_3, will respond dramatically to O_3 exposure.

Ultimately, a complex set of mechanisms activated to varying degrees and acting differently in different individuals will determine susceptibility or sensitivity. For example, bronchoconstriction induced by several mechanisms may be blocked accordingly by different agents, such as β_2 agonists, anti-inflammatory agents, methyl-xanthines, membrane or receptor agonists, catecholamine agents, and prostaglandins. Unfortunately, little information on these aspects of the study population is available so that reliance must be placed on limited work-ups, non-standardized clinical evaluations and definitions, and theoretical considerations. Thus, estimates of "at-risk" populations are difficult if not impossible to assess with any precision.

Various anthropomorphic and demographic characteristics have been used to try to characterize susceptible individuals in the general population. Gender differences, especially for children; age differences, especially between the very young and the very old; and possibly racial or ethnic differences, such as differences in nutritional status, differences in baseline lung function, or differences in immunological status, may predispose individuals to susceptibility or sensitivity to ozone, since all of these factors have well-known implications for infectious and chronic diseases and immunological states. None of these factors, however, has been sufficiently studied in relation to O_3 exposure to give definitive answers.

The most prominent modifier of response to O_3 in the general population is minute ventilation, which increases proportionately with increases in exercise workload. Higher levels of exercise enhance the likelihood of increased frequency of irritative symptoms and decrements in forced expiratory volume and flow. Unfortunately, even in a well-controlled experiment on a homogeneous group of subjects, physiological responses to the same exercise levels and the same O_3 concentrations will vary widely among individuals.

Exposure history may determine susceptibility or sensitivity. Smokers may be more or less sensitive. They are more susceptible to impaired defense against infection, they have some chronic inflammation in the airways, they have cellular damage, and they may have altered biochemical/cellular responses (e.g., reduced trypsin inhibitory capacity, neutrophilia, impaired macrophage activity). Likewise, those with "significant" occupational exposures to irritants or sensitizers or allergens may have similar predispositions. Furthermore, both groups show differential immunological status, atopy, and, in some cases, bronchomotor tone. Despite these inferences, there is some evidence to suggest that smokers may be less sensitive to O_3, although data are available only from a limited number of studies and are inconclusive.

Social, cultural, and economic factors, especially as they affect nutritional status (e.g., vitamin E intake, anemia), may be important. While animal studies with vitamin E indicate that differential responses may be related to nutrition, no evidence exists to indicate that man would benefit from increased vitamin E intake in relation to ambient ozone exposures.

Another determinant of sensitivity is preexisting disease. Asthmatics, who have variable airflow obstruction or reversible airway reactivity, or both, and who may have altered immunological states (e.g., atopy, increased immunoglobulin-E, possibly prostaglandin function and/or T-cell function) or cellular function (e.g., eosinophilia), may be potentially more sensitive to O_3. Defining an asthmatic, however, may be difficult. Likewise, allergic individuals, with a predisposing atopy, have altered immunological responses, similar to asthmatics, and may have labile bronchomotor tone, such that they may be considered to be potentially more sensitive. Patients with COLD may or may not be potentially more sensitive to O_3. Although currently available evidence indicates that individuals with preexisting disease respond to O_3 exposure to a similar degree as normal subjects, appropriate inclusion and exclusion criteria for selection of these subjects, especially better clinical diagnoses validated by pulmonary function, must be considered before their sensitivity to O_3 can be adequately determined. Nevertheless, one question that arises is whether or not small functional changes in individuals with COLD, asthma, or allergy represent equivalent physiological significance compared to the normal subject.

13.7.3 Potentially At-Risk Subpopulations

As the preceding discussion clearly indicates, definitive data on the relative susceptibilities to ozone of various kinds of individual subjects are lacking, both in epidemiological and controlled-exposure studies. Notwithstanding the uncertainties that exist in the data, it is possible to identify three major subpopulations that may be at particular risk from exposure to ozone.

In the Clean Air Act, the definition of a "sensitive population" excludes "individuals who are otherwise dependent on a controlled internal environment" and includes "particularly sensitive citizens . . . who in the normal course of daily activity are exposed to the ambient environment." Early research demonstrated that the respiratory system is affected by exposure to certain air pollutants, including ozone, nitrogen dioxide, and other oxidants. As a consequence, Congress took note of pollutant effects on the respiratory system and gave bronchial asthmatics and emphysematics as examples of "particularly sensitive" individuals. With regard to research on health effects, Congress has noted that attention should go beyond "normal segments of the population to effects on the very young, the aged, the infirm, and other susceptible individuals." Concern should be given to the "contribution of age, ethnic, social, occupational, smoking, and other factors to susceptibility to air pollution agents."

Consonant with the provisions of the Clean Air Act and with its legislative history, the first major subpopulation that appears to be at particular risk from exposure to ozone is that subgroup of the general population characterized as having preexisting disease. Available data on actual differences in sensitivity between these and healthy, normal members of the general population indicate that under the exposure regimes used to date, individuals with preexisting disease may not be more sensitive to ozone than normal individuals. Nevertheless, two considerations place these individuals among subpopulations at potential risk from exposure to ozone. First, it must be noted that concern with triggering untoward reactions has necessitated the use of low concentrations and low exercise levels in most studies on subjects with preexisting disease. Therefore, few or no data on responses at higher concentrations and higher exercise levels are available for comparison with responses in normal subjects. Thus, definitive data on responses in individuals with preexisting disease are not available and may not even become available. Second, however, it must be emphasized that in individuals with already compromised pulmonary function, the decrements in function produced by exposure to ozone, while similar to or even the same as those experienced by normal subjects, represent a further decline in volumes and flows that are already diminished. Such declines may be expected to impair further the ability to perform normal activities. In individuals with preexisting diseases such as asthma or allergies, increases in symptoms upon exposure to ozone, above and beyond symptoms seen in the general population, may also impair or further curtail the ability to function normally.

A second major subpopulation at apparent special risk from exposure to ozone consists of individuals ("responders") in the general population, not yet characterized medically except for their responses to ozone, who experience greater decrements in lung function from exposure to ozone than those observed in the remainder of the general population. As yet no means of determining in advance those members of the general population who are "responders" has been devised. It is important to note here what has been discussed previously in this chapter and in chapter 11; that is, group means presented in chapter 11 and in Figures 13-2 through 13-5 (and Table 13-3) include values for the "responders" in the respective study cohorts of otherwise healthy, normal subjects. Although no means of identifying the number or demographic characteristics of "responders" exists, they are clearly a subgroup of the general population whose individual members appear to be at particular risk from exposure to ozone.

Data presented in Chapter 11 and in this chapter underscore the importance of exercise in the potentiation of effects from exposure to ozone. Thus, a third major subpopulation potentially at risk from exposure to ozone is composed of those individuals (healthy or otherwise) whose activities out of doors, whether vocational or avocational, result in increases in minute ventilation. As stated in section 13.7.2, "the most prominent modifier of response to O_3 in the general population is minute ventilation, which increases proportionately with increases in exercise workload." Although many individuals with preexisting disease would not be expected to exercise at the same levels one would expect in healthy individuals, any increase in activity level would bring about a commensurate increase in minute ventilation.

As pointed out throughout this chapter, other biological and nonbiological factors are suspected of influencing responses to ozone. Data remain inconclusive at the present, however, regarding the importance of age, gender, and other factors in influencing response to ozone. Thus, at the present time, no other subpopulations are thought to be biologically predisposed to increased sensitivity to ozone. To the extent that the aged, the young, males, or females participate in activities out of doors that raise their minute ventilations, all of these subgroups may be considered to be potentially at risk, depending upon other determinants of total ozone dose, O_3 concentration and exposure duration.

13.7.4 Demographic Distribution of the General Population

The U.S. Bureau of the Census periodically provides an updated statistical summary of the U.S. population by conducting a decennial survey, supplemented by monthly surveys of representative population samples. The complete census represents a total count of the population since an attempt is made to account for the social, economic, and housing characteristics of every residence. In determining residence, the census counts each person as an inhabitant of a usual place where eating and sleeping take place rather than a person's legal or voting residence. Each residence is, in turn, grouped according to the official standard metropolitan statistical areas (SMSA's) and standard consolidated statistical areas (SCSA's) as defined by the Office of Management and Budget. Briefly, SMSA's represent a large population nucleus together with adjacent communities which have a high degree of social and economic integration; SCSA's are large metropolitan complexes consisting of groups of closely related adjacent SMSA's. Table 13-6 gives the geographical distribution of the resident population of the United States for 1980 (U.S. Bureau of the Census, 1982). The entire territory of the U.S. is classified as metropolitan (inside SMSA's) or nonmetropolitan (outside SMSA's). According to the 1980 census, the urban population comprises all persons living in cities, villages, boroughs, and towns of 2500 or more inhabitants. Additional data on age, sex, and race obtained from the 1980 census are shown in Table 13-7. Evaluation of previous census data indicated a total net underenumeration rate of about 2.2 percent in 1970 and 2.7 percent in 1960. Although estimates for 1980 have

TABLE 13-6. GEOGRAPHICAL DISTRIBUTION OF THE RESIDENT POPULATION OF THE UNITED STATES, 1980[a]

Residence	Population, millions	Population, percent
Total	226.5	100.0
Northeast	49.1	21.7
North Central	58.9	26.0
South	75.4	33.3
West	43.2	19.0
Metropolitan areas[b]	169.4	74.8
Central cities	68.0	30.0
Outside central cities	101.5	44.8
Nonmetropolitan areas	57.1	25.2
Urban[c]	167.1	73.7
Rural	59.5	26.3

[a] U.S. Bureau of the Census (1982).

[b] Represented by 318 standard metropolitan statistical areas (SMSA's).

[c] Comprises all persons living in cities, villages, boroughs, and towns of 2500 or more inhabitants but excluding those persons living in the rural portions of extended cities.

not been published, preliminary results indicated that overall coverage improved in the 1980 census. Census data presented in Tables 13-6 and 13-7 have not been adjusted for underenumeration.

13.7.5 Demographic Distribution of Individuals with Chronic Respiratory Conditions

Certain subpopulations have been identified as potentially-at-risk to ozone or photochemical oxidant exposure by virtue of preexisting respiratory conditions like chronic obstructive lung disease (COLD), asthma, and upper respiratory allergies. Each year the National Health Interview Survey (HIS) conducted by the National Center for Health Statistics (NCHS) reports the prevalence of chronic respiratory conditions in the United States. These conditions are classified by type, according to the Ninth Revision of the International Classification of Diseases adopted for use in the United States (World Health Organization, 1977). According to NCHS, a condition is considered

TABLE 13-7. TOTAL POPULATION OF THE UNITED STATES BY AGE, SEX, AND RACE, 1980[a]

Age, sex, race	Population, millions	Population, percent
Total	226.5	100.0
Under 5 years	16.3	7.2
5-17 years	47.1	20.8
18-44 years	93.3	41.2
45-64 years	44.4	19.6
65 years and over	25.5	11.3
Male	110.0	48.6
Female	116.5	51.4
White[b]	194.8	86.0
Black[b]	26.6	11.7
Other[b]	5.1	2.3

[a] U.S. Bureau of the Census (1982).

[b] Data represent self-classification according to 15 groups listed on the 1980 census questionnaire: White, Black, American, Indian, Eskimo, Aleut, Chinese, Filipino, Japanese, Asian Indian, Korean, Vietnamese, Hawaiian, Samoan, Guamanian, and Other.

to be chronic if it had been documented by a physician more than three months before the interview was conducted. In the HIS for 1979 (U.S. Department of Health and Human Services, 1981) COLD was not listed as a specific medical condition since it is a clinical term and not generally recognized by the general public. However, this term has been used with increasing frequency by physicians rather than the more common terms chronic bronchitis and emphysema in classifying chronic airways obstruction. As a result, there may be an underestimation by the HIS of the true prevalence of this disorder.

The estimated prevalence of chronic bronchitis, emphysema, and asthma in the United States is shown in Table 13-8 for the year 1979 (U.S. Department of Health and Human Services, 1981). All three respiratory conditions combined accounted for over 16 million individuals in 1979, representing 7.5 percent of the population. Approximately one-third of the individuals with chronic bronchitis and asthma were under 17 years of age. An additional 15 to 16 million persons reported having hay fever and other upper respiratory allergies. Accounting for an underestimation by the HIS, the total number of individuals

TABLE 13-8. PREVALENCE OF CHRONIC RESPIRATORY CONDITIONS BY SEX AND AGE FOR 1979[a]

	Number of persons, in thousands							
Condition[b]	Total[c]	Male	Female	<17 years old	17-44 years old	45-64 years old	≥65 years old	% of U.S. population
Chronic bronchitis	7474	3289	4175	2458	2412	1547	1060	3.5
Emphysema	2137	1364	770	12[d]	127[d]	1008	990	1.0
Asthma[e]	6402	3113	3293	2225	2203	1482	488	3.0
Hay fever and other upper respiratory allergies[f]	15,620	7027	8584	3151	8278	3012	1181	7.2

[a] U.S. Department of Health and Human Services, 1981.

[b] Classified by type, according to the Ninth Revision of the International Classific of Diseases (World Health Organization, 1977).

[c] Reported as actual number in thousands; remaining subsets have been calculated from percentages and are rounded off.

[d] Does not meet standards of reliability or precision set by the National Center for Health Statistics (more than 30% relative standard error).

[e] With or without hay fever.

[f] Without asthma.

with documented and undocumented respiratory conditions in the United States is estimated to be at least 47 million, which is approximately 20 percent of the population.

13.8 SUMMARY AND CONCLUSIONS

Controlled human studies of at-rest exposures to O_3 lasting 2 to 4 hr have demonstrated decrements in forced expiratory volume and flow occurring at and above 0.5 ppm of O_3. Airway resistance was not changed at these O_3 concentrations. Breathing O_3 at rest at concentrations < 0.5 ppm did not significantly impair pulmonary function although the occurrence of some O_3-related pulmonary symptoms has been suggested in a number of studies.

One of the principal modifiers of the magnitude of response to O_3 is minute ventilation ($\dot{V}_E$), which increases proportionately with increases in exercise work load. Adjustment by the respiratory system to an increased work load is characterized by increased frequency and depth of breathing. Consequent increases in $\dot{V}_E$ not only increase the overall volume of inhaled pollutant, but such ventilatory patterns also promote a deeper penetration of ozone into the peripheral lung, which is the region most sensitive to ozone and where a greater absorption of ozone will occur. These processes are further enhanced at high work loads ($\dot{V}_E > 35$ L/min), since the mode of breathing will most likely change at that $\dot{V}_E$ from nasal to oronasal.

Even in well-controlled experiments on a homogeneous group of subjects, physiological responses to the same work and pollutant loads will vary widely among individuals. Despite such large interindividual variability, the magnitude of group mean lung function changes is positively associated with the level of exercise and ozone concentration. Based on reported studies of 1 to 3 hr duration, significant pulmonary function impairment (decrement) occurs when exercise is combined with exposure to ozone:

1. Light exercise ($\dot{V}_E \leq 25$ L/min) - Effects at ≥ 0.37 ppm O_3;
2. Moderate exercise ($\dot{V}_E = 26$ to 43 L/min) - Effects at ≥ 0.30 ppm O_3;
3. Heavy exercise ($\dot{V}_E = 44$ to 63 L/min) - Effects at ≥ 0.24 ppm O_3; and
4. Very heavy exercise ($\dot{V}_E \geq 64$ L/min) - Effects at ≥ 0.18 ppm O_3, with suggestions of decrements at 0.12 ppm O_3.

For the majority of the controlled studies, 15-min intermittent exercise alternated with 15-min rest was employed for the duration of the exposure. Continuous exercise equivalent in duration to the sum of intermittent exercise periods at comparable ozone concentrations (0.2 to 0.4 ppm) and minute ventilation (60 to 80 L/min) seems to elicit about the same changes in pulmonary function. The maximum response to O_3 exposure can be observed within 5 to 10 min following the end of each exercise period. Functional recovery, at least from a single exposure with exercise, appears to progress in two phases: during the initial rapid phase, lasting between 1 and 3 hr, pulmonary function improves more than 50 percent; this is followed by a much slower recovery that is usually completed within 24 hr. In some individuals, despite apparent functional recovery, other regulatory systems may still exhibit abnormal responses when stimulated; e.g., airway hyperreactivity might persist for days.

A close association has been observed between changes in pulmonary function and the occurrence of respiratory symptoms in response to acute exposure to O_3. This association holds for both the time-course and magnitude of effects. The symptoms found in association with clinical exposure to O_3 alone and with exposure to photochemical air pollution are similar but not identical. Eye irritation, one of the most common complaints associated with photochemical pollution, is not characteristic of clinical exposures to O_3, even at concentrations several times higher than any likely to be encountered in ambient air. There is also evidence to suggest that other symptoms, indicative of either upper or lower respiratory tract irritation, are more likely to occur in populations exposed to ambient air pollution than in subjects exposed to O_3 alone in chamber studies. For example, cough has been reported at 0.08 ppm O_3 and at 0.10 ppm oxidants in epidemiological studies and during clinical exposure to 0.12 ppm O_3; nose and throat irritation have been reported in community studies in association with 0.10 ppm oxidants but not at or below 0.15 ppm O_3 in laboratory studies. Between 0.15 and 0.30 ppm, a variety of both respiratory and nonrespiratory symptoms have been reported in controlled exposures. They include throat dryness, difficulty or pain during deep inspiration, chest tightness, substernal soreness or pain, wheezing, lassitude, malaise, and nausea. Symptoms are therefore considered to be useful adjuncts in assessing the effects of O_3 and photochemical pollution, particularly if combined with objective measures of lung function.

Only a few studies have been designed to examine the effects of O_3 on exercise performance. In one study, very heavy exercise ($\dot{V}_E$ > 64 L/min) at a high O_3 concentration (0.75 ppm) reduced postexposure maximal exercise capacity by limiting maximal oxygen consumption; submaximal oxygen consumption changes were inconsistent. The extent of ventilatory and respiratory metabolic changes observed during or following the exposure appears to have been related to the magnitude of pulmonary function impairment. Whether such changes are consequent to respiratory discomfort (i.e., symptomatic effects) or are the result of changes in lung mechanics or both is still unclear and needs to be elucidated.

Environmental conditions such as heat and relative humidity may enhance subjective symptoms and physiological impairment following O_3 exposure. Modification of the effects of O_3 by these factors may be attributed to increased ventilation which, like exercise, increases the overall volume of inhaled pollutant and promotes greater penetration into peripheral areas of the lung.

Additional factors suspected of altering sensitivity to ozone are numerous. For example, age differences, especially between the very young and the very old; gender differences, especially for children; personal habits such as cigarette smoking; and possibly social, cultural, or economic factors such as differences in nutritional status or differences in immunological status may predispose individuals to susceptibility to ozone. Those actually known to alter sensitivity, however, are few, largely because they have not been examined adequately to determine definitively their effects on sensitivity to O_3. The following briefly summarizes what is actually known from the data regarding the importance of these factors:

1. Age. Although changes in growth and development of the lung with age have been postulated as one of many factors capable of modifying responsiveness to O_3, studies have not been designed to test adequately for effects of O_3 in different age groups.

2. Sex. Sex differences in responsiveness to ozone have not been adequately studied. Lung function of women, as assessed by changes in $FEV_{1.0}$, appears to be affected more than that of men under similar exercise and exposure conditions, but the differences have not been analyzed systematically. Further research is needed to determine whether differences in lung volumes or differences in exercise capacity during exposure may lead to sex differences in responses to O_3.

3. Smoking Status. Differences between smokers and nonsmokers have been studied often, but the data are not documented well and are often confusing. Published results indicate a discrepancy in findings. There is some evidence, however, to suggest that smokers may be less sensitive to O_3.

4. Nutritional Status. Antioxidant properties of vitamin E in preventing ozone-initiated peroxidation *in vitro* are well demonstrated and their protective effects *in vivo* are clearly demonstrated in rats and mice. No evidence indicates, however, that man would benefit from increased vitamin E intake relative to ambient ozone exposures.

5. Red Blood Cell Enzyme Deficiencies. There have been too few studies performed to document reliably that individuals with a hereditary deficiency of glucose-6-phosphate dehydrogenase may be at-risk to significant hematological effects from O_3 exposure.

Successive daily brief exposures of healthy human subjects to O_3 (<0.7 ppm for approximately 2 hr) induce a typical temporal pattern of response. Maximum functional changes that occur after the first or second exposure day become progressively attenuated on each of the subsequent days. By the fourth day of exposure, the effects are, on the average, not different from those observed following control (air) exposure. Individuals need between 3 and 7 days to develop full attenuation, with more sensitive subjects requiring more time. The magnitude of a peak response to O_3 appears to be directly related to its concentration. In addition, concentrations of O_3 that have no detectable effect appear not to invoke changes in response to subsequent exposures at higher O_3 concentrations. Full attenuation, even in ozone-sensitive subjects, does not persist for more than 3 to 7 days in most individuals, while partial attenuation might persist for up to 2 weeks. Although symptomatic response is generally related to the magnitude of the functional response, partial symptomatic attenuation appears to persist longer, for up to 4 weeks.

Whether populations exposed to photochemical air pollution develop at least partial attenuation is unknown. No epidemiological studies have been designed to test this hypothesis. While there is limited information obtained from controlled laboratory studies to support this hypothesis, additional information is required.

Responses to O_3, whether functional, biochemical, or morphological, have the potential for altering responses in both man and laboratory animals during repeated or continuous exposure. At present, the underlying mechanisms for this response are poorly understood and the effectiveness of such mitigating forces in protecting the long-term health of the individual against O_3 is still uncertain. Therefore, hyperresponsiveness to O_3, including changes in bronchial reactivity, and the subsequent attenuation of responsiveness may be viewed as sequential states in a continuing process.

Several animal experiments have demonstrated increased susceptibility to respiratory infections following O_3 exposure. Thus, it could be hypothesized that humans exposed to O_3 could experience decrements in their host defenses against infection. At the present time, however, these effects have not been described in humans exposed to O_3, so that concentrations at which effects might occur in man or the severity of such effects are unknown and difficult to predict.

Animal studies have also reported a number of extrapulmonary responses to O_3, including cardiovascular, reproductive, and teratological effects, along with changes in endocrine function. The implications of these findings for human health are difficult to judge at the present time. In addition, central nervous system effects, alterations in red blood cell morphology and enzymatic activity, as well as chromosomal effects on circulating lymphocytes, have been observed in man and laboratory animals following exposure to high concentrations of O_3. It is unlikely, however, that these changes would have any functional significance in humans when exposure schedules are used that are representative of exposures that the population at large might actually experience.

Currently available evidence indicates that individuals with preexisting disease respond to O_3 exposure to a similar degree as normal subjects. Patients with chronic obstructive lung disease and/or asthma have not shown increased sensitivity to O_3 in controlled human exposure studies, but there is some indication from epidemiological studies that asthmatics may be symptomatically and possibly functionally more sensitive than healthy individuals to ambient air exposures. Appropriate inclusion and exclusion criteria for selection of these subjects, however, especially better clinical diagnoses validated by pulmonary function, must be considered before their sensitivity to O_3 can be adequately determined. None of these factors has been sufficiently studied in relation to O_3 exposures to give definitive answers. Thus, estimates of at-risk populations are difficult to assess with any precision.

Despite wide variations in study techniques and experimental designs, acute and subchronic exposures of animals to levels of ozone < 0.5 ppm produce similar types of responses in all species examined. A characteristic inflammatory lesion occurs at the junction of the conducting airways and the gas-exchange regions of the lung after acute O_3 exposure. Dosimetry model simulations predict that the maximal tissue dose of O_3 occurs in this region of the lung. Continuation of the inflammatory process during longer O_3 exposures is especially important since it appears to be correlated with increased lung collagen content and remodeling of the centriacinar airways. There is no evidence of emphysema, however, in the lungs of animals exposed to O_3 for prolonged periods of time.

Controlled human and animal exposures have not consistently demonstrated any enhancement of respiratory effects for combined exposures of O_3 with SO_2, NO_2, CO, or H_2SO_4 and other particulate aerosols. Ozone alone is considered to be responsible for the observed effects of those combinations or of multiple mixtures of these pollutants. In addition, there have been far too few controlled toxicological studies with other oxidants, such as peroxyacetyl nitrate or hydrogen peroxide, to permit any sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. Nevertheless, there is still some concern that combinations of oxidant pollutants with other pollutants may contribute to the symptom aggravation and decreased lung function described in epidemiological studies on individuals with asthma and in children and young adults. For this reason, the effects of interaction between inhaled oxidant gases and other environmental pollutants on the lung need to be systematically studied using exposure regimens that are more closely representative of ambient air ratios of peak concentrations, frequency, duration, and time intervals between events.

Despite uncertainties that may exist in the data, it is possible to identify three major subpopulations that may be at particular risk from exposure to ozone, based on known health effects, activity patterns, personal habits, and actual or potential exposures to ozone.

The first major subpopulation that appears to be at particular risk from exposure to ozone is that subgroup of the general population characterized as having preexisting disease. Available data on actual differences in sensitivity between these and healthy, normal members of the general population indicate that under the exposure regimes used to date individuals with preexisting disease may not be more sensitive to ozone than normal individuals. Nevertheless, two considerations place these individuals among subpopulations at potential risk from exposure to ozone. First, it must be noted that concern with triggering untoward reactions has necessitated the use of low concentrations and low exercise levels in most studies on subjects with preexisting disease. Therefore, few or no data on responses at higher concentrations and higher exercise levels are available for comparison with responses in normal subjects. Thus, definitive data on responses in individuals with preexisting disease are not available and may not ever become available. Second, however, it must be emphasized that in individuals with already compromised pulmonary function, the decrements in function produced by exposure to ozone, while similar to or even the same as those experienced by normal subjects, represent a further decline in volumes and flows that are already diminished. Such declines may be expected to impair further the ability to perform normal activities. In individuals with preexisting diseases such as asthma or allergies, increases in symptoms upon exposure to ozone, above and beyond symptoms seen in the general population, may also impair or further curtail the ability to function normally.

A second major subpopulation at apparent special risk from exposure to ozone consists of individuals ("responders") in the general population, not yet characterized medically except for their responses to ozone, who experience greater decrements in lung function from exposure to ozone than those observed in the remainder of the general population. As yet no means of determining in advance those members of the general population who are "responders" has been devised.

Data presented in this chapter underscore the importance of exercise in the potentiation of effects from exposure to ozone. Thus, a third major subpopulation potentially at risk from exposure to ozone is composed of those individuals (healthy and otherwise) whose activities out of doors, whether vocational or avocational, result in increases in minute ventilation. Although many individuals with preexisting disease would not be expected to exercise at the same levels one would expect in healthy individuals, any increase in activity level would bring about a commensurate increase in minute ventilation. To the extent that the aged, the young, males, or females participate in activities out of doors that raise their minute ventilations, all of these subgroups may be considered to be potentially at risk, depending upon other determinants of total ozone dose, O_3 concentration, and exposure duration.

Other biological and nonbiological factors are suspected of influencing responses to ozone. Data remain inconclusive at the present, however, regarding the importance of age, gender, and other factors in influencing response to ozone. Thus, at the present time, no other subpopulations are thought to be biologically predisposed to increased sensitivity to ozone. It must be emphasized, however, that the final identification of those effects that are considered "adverse" and the final identification of "at-risk" populations are both the domain of the Administrator.

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APPENDIX A: GLOSSARY OF PULMONARY TERMS AND SYMBOLS*

Acetylcholine (ACh): A naturally occurring substance in the body having important parasympathetic effects; often used as a bronchoconstrictor.

Aerosol: Solid particles or liquid droplets that are dispersed or suspended in a gas, ranging in size from 10^{-4} to 10^{2} micrometers (µm).

Air spaces: All alveolar ducts, alveolar sacs, and alveoli. To be contrasted with AIRWAYS.

Airway conductance (Gaw): Reciprocal of airway resistance. Gaw = (1/Raw).

Airway resistance (Raw): The (frictional) resistance to airflow afforded by the airways between the airway opening at the mouth and the alveoli.

Airways: All passageways of the respiratory tract from mouth or nares down to and including respiratory bronchioles. To be contrasted with AIR SPACES.

Allergen: A material that, as a result of coming into contact with appropriate tissues of an animal body, induces a state of allergy or hypersensitivity; generally associated with idiosyncratic hypersensitivities.

Alveolar-arterial oxygen pressure difference [$P(A-a)O_2$]: The difference in partial pressure of O_2 in the alveolar gas spaces and that in the systemic arterial blood, measured in torr.

Alveolar-capillary membrane: A fine membrane (0.2 to 0.4 µm) separating alveolus from capillary; composed of epithelial cells lining the alveolus, a thin layer of connective tissue, and a layer of capillary endothelial cells.

Alveolar carbon dioxide pressure (P_ACO_2): Partial pressure of carbon dioxide in the air contained in the lung alveoli.

Alveolar oxygen partial pressure (P_AO_2): Partial pressure of oxygen in the air contained in the alveoli of the lungs.

Alveolar septum (pl. septa): A thin tissue partition between two adjacent pulmonary alveoli, consisting of a close-meshed capillary network and interstitium covered on both surfaces by alveolar epithelial cells.

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Alveolitis: (interstitial pneumonia): Inflammation of the lung distal to the terminal non-respiratory bronchiole. Unless otherwise indicated, it is assumed that the condition is diffuse. Arbitrarily, the term is not used to refer to exudate in air spaces resulting from bacterial infection of the lung.

Alveolus: Hexagonal or spherical air cells of the lungs. The majority of alveoli arise from the alveolar ducts which are lined with the alveoli. An alveolus is an ultimate respiratory unit where the gas exchange takes place.

Anatomical dead space ($V_{D\ anat}$): Volume of the conducting airways down to the level where, during air breathing, gas exchange with blood can occur, a region probably situated at the entrance of the alveolar ducts.

Arterial oxygen saturation (SaO_2): Percent saturation of dissolved oxygen in arterial blood.

Arterial partial pressure of carbon dioxide ($PaCO_2$): Partial pressure of dissolved carbon dioxide in arterial blood.

Arterial partial pressure of oxygen (PaO_2): Partial pressure of dissolved oxygen in arterial blood.

Asthma: A disease characterized by an increased responsiveness of the airways to various stimuli and manifested by slowing of forced expiration which changes in severity either spontaneously or as a result of therapy. The term asthma may be modified by words or phrases indicating its etiology, factors provoking attacks, or its duration.

Atelectasis: State of collapse of air spaces with elimination of the gas phase.

ATPS condition (ATPS): Ambient temperature and pressure, saturated with water vapor. These are the conditions existing in a water spirometer.

Atropine: A poisonous white crystalline alkaloid, $C_{17}H_{23}NO_3$, from belladonna and related plants, used to relieve spasms of smooth muscles. It is an anticholinergic agent.

Breathing pattern: A general term designating the characteristics of the ventilatory activity, e.g., tidal volume, frequency of breathing, and shape of the volume time curve.

Breuer-Hering reflexes (Hering-Breuer reflexes): Ventilatory reflexes originating in the lungs. The reflex arcs are formed by the pulmonary mechanoreceptors, the vagal afferent fibers, the respiratory centers, the medullospinal pathway, the motor neurons, and the respiratory muscles. The afferent link informs the respiratory centers of the volume state or of the rate of change of volume of the lungs. Three types of Breuer-Hering reflexes have been described: 1) an inflation reflex in which lung inflation tends to inhibit inspiration and stimulate expiration; 2) a deflation reflex in which lung deflation tends to inhibit expiration and stimulate inspiration; and 3) a "paradoxical reflex," described but largely disregarded by Breuer and Hering, in which sudden inflation may stimulate inspiratory muscles.

Bronchiole: One of the finer subdivisions of the airways, less than 1 mm in diameter, and having no cartilage in its wall.

Bronchiolitis: Inflammation of the bronchioles which may be acute or chronic. If the etiology is known, it should be stated. If permanent occlusion of the lumens is present, the term bronchiolitis obliterans may be used.

Bronchitis: A non-neoplastic disorder of structure or function of the bronchi resulting from infectious or noninfectious irritation. The term bronchitis should be modified by appropriate words or phrases to indicate its etiology, its chronicity, the presence of associated airways dysfunction, or type of anatomic change. The term chronic bronchitis, when unqualified, refers to a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucous hypersecretion and certain structural alterations in the bronchi. Anatomic changes may include hypertrophy of the mucous-secreting apparatus and epithelial metaplasia, as well as more classic evidences of inflammation. In epidemiologic studies, the presence of cough or sputum production on most days for at least three months of the year has sometimes been accepted as a criterion for the diagnosis.

Bronchoconstrictor: An agent that causes a reduction in the caliber (diameter) of airways.

Bronchodilator: An agent that causes an increase in the caliber (diameter) of airways.

Bronchus: One of the subdivisions of the trachea serving to convey air to and from the lungs. The trachea divides into right and left main bronchi which in turn form lobar, segmental, and subsegmental bronchi.

BTPS conditions (BTPS): Body temperature, barometric pressure, and saturated with water vapor. These are the conditions existing in the gas phase of the lungs. For man the normal temperature is taken as 37°C, the pressure as the barometric pressure, and the partial pressure of water vapor as 47 torr.

Carbachol: A parasympathetic stimulant (carbamoylcholine chloride, $C_6H_{15}ClN_2O_2$) that produces constriction of the bronchial smooth muscles.

Carbon dioxide production ($\dot{V}CO_2$): Rate of carbon dioxide production by organisms, tissues, or cells. Common units: ml CO_2 (STPD)/kg·min.

Carbon monoxide (CO): An odorless, colorless, toxic gas formed by incomplete combustion, with a strong affinity for hemoglobin and cytochrome; it reduces oxygen absorption capacity, transport, and utilization.

Carboxyhemoglobin (COHb): Hemoglobin in which the iron is associated with carbon monoxide. The affinity of hemoglobin for CO is about 300 times greater than for O_2.

Chronic obstructive lung disease (COLD): This term refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration. It is recommended that a more specific term, such as chronic obstructive bronchitis or chronic obstructive emphysema, be used whenever possible. Synonymous with chronic obstructive pulmonary disease (COPD).

Closing capacity (CC): Closing volume plus residual volume, often expressed as a ratio of TLC, i.e. (CC/TLC%).

Closing volume (CV): The volume exhaled after the expired gas concentration is inflected from an alveolar plateau during a controlled breathing maneuver. Since the value obtained is dependent on the specific test technique, the method used must be designated in the text, and when necessary, specified by a qualifying symbol. Closing volume is often expressed as a ratio of the VC, i.e. (CV/VC%).

Collateral resistance (R_{coll}): Resistance to flow through indirect pathways. See COLLATERAL VENTILATION and RESISTANCE.

Collateral ventilation: Ventilation of air spaces via indirect pathways, e.g., through pores in alveolar septa, or anastomosing respiratory bronchioles.

Compliance (C_L,C_{st}): A measure of distensibility. Pulmonary compliance is given by the slope of a static volume-pressure curve at a point, or the linear approximation of a nearly straight portion of such a curve, expressed in liters/cm H_2O or ml/cm H_2O. Since the static volume-pressure characteristics of lungs are nonlinear (static compliance decreases as lung volume increases) and vary according to the previous volume history (static compliance at a given volume increases immediately after full inflation and decreases following deflation), careful specification of the conditions of measurement are necessary. Absolute values also depend on organ size. See also DYNAMIC COMPLIANCE.

Conductance (G): The reciprocal of RESISTANCE. See AIRWAY CONDUCTANCE.

Diffusing capacity of the lung (D_L, D_LO_2, D_LCO_2, D_LCO): Amount of gas (O_2, CO, CO_2) commonly expressed as ml gas (STPD) diffusing between alveolar gas and pulmonary capillary blood per torr mean gas pressure difference per min, i.e., ml O_2/(min-torr). Synonymous with transfer factor and diffusion factor.

Dynamic compliance (C_{dyn}): The ratio of the tidal volume to the change in intrapleural pressure between the points of zero flow at the extremes of tidal volume in liters/cm H_2O or ml/cm H_2O. Since at the points of zero airflow at the extremes of tidal volume, volume acceleration is usually other than zero, and since, particularly in abnormal states, flow may still be taking place within lungs between regions which are exchanging volume, dynamic compliance may differ from static compliance, the latter pertaining to condition of zero volume acceleration and zero gas flow throughout the lungs. In normal lungs at ordinary volumes and respiratory frequencies, static and dynamic compliance are the same.

Elastance (E): The reciprocal of COMPLIANCE; expressed in cm H_2O/liter or cm H_2O/ml.

Electrocardiogram (ECG, EKG): The graphic record of the electrical currents that are associated with the heart's contraction and relaxation.

Expiratory reserve volume (ERV): The maximal volume of air exhaled from the end-expiratory level.

FEV_t/FVC: A ratio of timed (t = 0.5, 1, 2, 3 s) forced expiratory volume (FEV_t) to forced vital capacity (FVC). The ratio is often expressed in percent 100 x FEV_t/FVC. It is an index of airway obstruction.

Flow volume curve: Graph of instantaneous forced expiratory flow recorded at the mouth, against corresponding lung volume. When recorded over the full vital capacity, the curve includes maximum expiratory flow rates at all lung volumes in the VC range and is called a maximum expiratory flow-volume curve (MEFV). A partial expiratory flow-volume curve (PEFV) is one which describes maximum expiratory flow rate over a portion of the vital capacity only.

Forced expiratory flow (FEFx): Related to some portion of the FVC curve. Modifiers refer to the amount of the FVC already exhaled when the measurement is made. For example:

$FEF_{75\%}$ = instantaneous forced expiratory flow after 75% of the FVC has been exhaled.

$FEF_{200-1200}$ = mean forced expiratory flow between 200 ml and 1200 ml of the FVC (formerly called the maximum expiratory flow rate (MEFR).

$FEF_{25-75\%}$ = mean forced expiratory flow during the middle half of the FVC [formerly called the maximum mid-expiratory flow rate (MMFR)].

FEF_{max} = the maximal forced expiratory flow achieved during an FVC.

Forced expiratory volume (FEV): Denotes the volume of gas which is exhaled in a given time interval during the execution of a forced vital capacity. Conventionally, the times used are 0.5, 0.75, or 1 sec, symbolized $FEV_{0.5}$, $FEV_{0.75}$, $FEV_{1.0}$. These values are often expressed as a percent of the forced vital capacity, e.g. ($FEV_{1.0}$/VC) X 100.

Forced inspiratory vital capacity (FIVC): The maximal volume of air inspired with a maximally forced effort from a position of maximal expiration.

Forced vital capacity (FVC): Vital capacity performed with a maximally forced expiratory effort.

Functional residual capacity (FRC): The sum of RV and ERV (the volume of air remaining in the lungs at the end-expiratory position). The method of measurement should be indicated as with RV.

Gas exchange: Movement of oxygen from the alveoli into the pulmonary capillary blood as carbon dioxide enters the alveoli from the blood. In broader terms, the exchange of gases between alveoli and lung capillaries.

Gas exchange ratio (R): See RESPIRATORY QUOTIENT.

Gas trapping: Trapping of gas behind small airways that were opened during inspiration but closed during forceful expiration. It is a volume difference between FVC and VC.

Hematocrit (Hct): The percentage of the volume of red blood cells in whole blood.

Hemoglobin (Hb): A hemoprotein naturally occurring in most vertebrate blood, consisting of four polypeptide chains (the globulin) to each of which there is attached a heme group. The heme is made of four pyrrole rings and a divalent iron (Fe^{2+}-protoporphyrin) which combines reversibly with molecular oxygen.

Histamine: A depressor amine derived from the amino acid histidine and found in all body tissues, with the highest concentration in the lung; a powerful stimulant of gastric secretion, a constrictor of bronchial smooth muscle, and a vasodilator that causes a fall in blood pressure.

Hypoxemia: A state in which the oxygen pressure and/or concentration in arterial and/or venous blood is lower than its normal value at sea level. Normal oxygen pressures at sea level are 85-100 torr in arterial blood and 37-44 torr in mixed venous blood. In adult humans the normal oxygen concentration is 17-23 ml O_2/100 ml arterial blood; in mixed venous blood at rest it is 13-18 ml O_2/100 ml blood.

Hypoxia: Any state in which the oxygen in the lung, blood, and/or tissues is abnormally low compared with that of normal resting man breathing air at sea level. If the P_{O2} is low in the environment, whether because of decreased barometric pressure or decreased fractional concentration of O_2, the condition is termed environmental hypoxia. Hypoxia when referring to the blood is termed hypoxemia. Tissues are said to be hypoxic when their P_{O2} is low, even if there is no arterial hypoxemia, as in "stagnant hypoxia" which occurs when the local circulation is low compared to the local metabolism.

Inspiratory capacity (IC): The sum of IRV and TV.

Inspiratory reserve volume (IRV): The maximal volume of air inhaled from the end-inspiratory level.

Inspiratory vital capacity (IVC): The maximum volume of air inhaled from the point of maximum expiration.

Kilogram-meter/min (kgm/min): The work performed each min to move a mass of 1 kg through a vertical distance of 1 m against the force of gravity. Synonymous with kilopond-meter/min.

Lung volume (V_L): Actual volume of the lung, including the volume of the conducting airways.

Maximal aerobic capacity (max $\dot{V}O_2$): The rate of oxygen uptake by the body during repetitive maximal respiratory effort. Synonymous with maximal oxygen consumption.

Maximum breathing capacity (MBC): Maximal volume of air which can be breathed per minute by a subject breathing as quickly and as deeply as possible. This tiring lung function test is usually limited to 12-20 sec, but given in liters (BTPS)/min. Synonymous with maximum voluntary ventilation (MVV).

Maximum expiratory flow ($\dot{V}_{max\ x}$): Forced expiratory flow, related to the total lung capacity or the actual volume of the lung at which the measurement is made. Modifiers refer to the amount of lung volume remaining when the measurement is made. For example:

$\dot{V}_{max\ 75\%}$ = instantaneous forced expiratory flow when the lung is at 75% of its TLC.

$\dot{V}_{max\ 3.0}$ = instantaneous forced expiratory flow when the lung volume is 3.0 liters

Maximum expiratory flow rate (MEFR): Synonymous with $FEF_{200-1200}$.

Maximum mid-expiratory flow rate (MMFR or MMEF): Synonymous with $FEF_{25-75\%}$.

Maximum ventilation (max $\dot{V}_E$): The volume of air breathed in one minute during repetitive maximal respiratory effort. Synonymous with maximum ventilatory minute volume.

Maximum voluntary ventilation (MVV): The volume of air breathed by a subject during voluntary maximum hyperventilation lasting a specific period of time. Synonymous with maximum breathing capacity (MBC).

Methemoglobin (MetHb): Hemoglobin in which iron is in the ferric state. Because the iron is oxidized, methemoglobin is incapable of oxygen transport. Methemoglobins are formed by various drugs and occur under pathological conditions. Many methods for hemoglobin measurements utilize methemoglobin (chlorhemiglobin, cyanhemiglobin).

Minute ventilation ($\dot{V}_E$): Volume of air breathed in one minute. It is a product of tidal volume (V_T) and breathing frequency (f_B). See VENTILATION.

Minute volume: Synonymous with minute ventilation.

Mucociliary transport: The process by which mucus is transported, by ciliary action, from the lungs.

Mucus: The clear, viscid secretion of mucous membranes, consisting of mucin, epithelial cells, leukocytes, and various inorganic salts suspended in water.

Nasopharyngeal: Relating to the nose or the nasal cavity and the pharynx (throat).

Nitrogen oxides: Compounds of N and O in ambient air; i.e., nitric oxide (NO) and others with a higher oxidation state of N, of which NO_2 is the most important toxicologically.

Nitrogen washout (ΔN_2, dN_2): The curve obtained by plotting the fractional concentration of N_2 in expired alveolar gas vs. time, for a subject switched from breathing ambient air to an inspired mixture of pure O_2. A progressive decrease of N_2 concentration ensues which may be analyzed into two or more exponential components. Normally, after 4 min of pure O_2 breathing the fractional N_2 concentration in expired alveolar gas is down to less than 2%.

Normoxia: A state in which the ambient oxygen pressure is approximately 150 ± 10 torr (i.e., the partial pressure of oxygen in air at sea level).

Oxidant: A chemical compound that has the ability to remove, accept, or share electrons from another chemical species, thereby oxidizing it.

Oxygen consumption ($\dot{V}O_2$, $\dot{Q}O_2$): Rate of oxygen uptake of organisms, tissues, or cells. Common units: ml O_2 (STPD)/(kg·min) or ml O_2 (STPD)/(kg·hr). For whole organisms the oxygen consumption is commonly expressed per unit surface area or some power of the body weight. For tissue samples or isolated cells $\dot{Q}_{O2}$ = µl O_2/hr per mg dry weight.

Oxygen saturation (SO_2): The amount of oxygen combined with hemoglobin, expressed as a percentage of the oxygen capacity of that hemoglobin. In arterial blood, SaO_2.

Oxygen uptake ($\dot{V}O_2$): Amount of oxygen taken up by the body from the environment, by the blood from the alveolar gas, or by an organ or tissue from the blood. When this amount of oxygen is expressed per unit of time one deals with an "oxygen uptake rate." "Oxygen consumption" refers more specifically to the oxygen uptake rate by all tissues of the body and is equal to the oxygen uptake rate of the organism only when the O_2 stores are constant.

Particulates: Fine solid particles such as dust, smoke, fumes, or smog, found in the air or in emissions.

Pathogen: Any virus, microorganism, or etiologic agent causing disease.

Peak expiratory flow (PEF): The highest forced expiratory flow measured with a peak flow meter.

Peroxyacetyl nitrate (PAN): Pollutant created by action of UV component of sunlight on hydrocarbons and NO_x in the air; an ingredient of photochemical smog.

Physiological dead space (V_D): Calculated volume which accounts for the difference between the pressures of CO_2 in expired and alveolar gas (or arterial blood). Physiological dead space reflects the combination of anatomical dead space and alveolar dead space, the volume of the latter increasing with the importance of the nonuniformity of the ventilation/perfusion ratio in the lung.

Plethysmograph: A rigid chamber placed around a living structure for the purpose of measuring changes in the volume of the structure. In respiratory measurements, the entire body is ordinarily enclosed ("body plethysmograph") and the plethysmograph is used to measure changes in volume of gas in the system produced 1) by solution and volatilization (e.g., uptake of foreign gases into the blood), 2) by changes in pressure or temperature (e.g., gas compression in the lungs, expansion of gas upon passing into the warm, moist lungs), or 3) by breathing through a tube to the outside. Three types of plethysmograph are used: a) pressure, b) volume, and c) pressure-volume. In type a, the body chambers have fixed volumes and volume changes are measured in terms of pressure change secondary to gas compression (inside the chamber, outside the body). In type b, the body chambers serve essentially as conduits between the body surface and devices (spirometers or integrating flowmeters) which measure gas displacements. Type c combines a and b by appropriate summing of chamber pressure and volume displacements.

Pneumotachograph: A device for measuring instantaneous gas flow rates in breathing by recording the pressure drop across a fixed flow resistance of known pressure-flow characteristics, commonly connected to the airway by means of a mouthpiece, face mask, or cannula. The flow resistance usually consists either of parallel capillary tubes (Fleisch type) or of fine-meshed screen (Silverman-Lilly type).

Pulmonary alveolar proteinosis: A chronic or recurrent disease characterized by the filling of alveoli with an insoluble exudate, usually poor in cells, rich in lipids and proteins, and accompanied by minimal histologic alteration of the alveolar walls.

Pulmonary edema: An accumulation of excessive amounts of fluid in the lung extravascular tissue and air spaces.

Pulmonary emphysema: An abnormal enlargement of the air spaces distal to the terminal nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls. The term emphysema may be modified by words or phrases to indicate its etiology, its anatomic subtype, or any associated airways dysfunction.

Residual volume (RV): That volume of air remaining in the lungs after maximal exhalation. The method of measurement should be indicated in the text or, when necessary, by appropriate qualifying symbols.

Resistance flow (R): The ratio of the flow-resistive components of pressure to simultaneous flow, in cm H_2O/liter per sec. Flow-resistive components of pressure are obtained by subtracting any elastic or inertial components, proportional respectively to volume and volume acceleration. Most flow resistances in the respiratory system are nonlinear, varying with the magnitude and direction of flow, with lung volume and lung volume history, and possibly with volume acceleration. Accordingly, careful specification of the conditions of measurement is necessary; see AIRWAY RESISTANCE, TISSUE RESISTANCE, TOTAL PULMONARY RESISTANCE, COLLATERAL RESISTANCE.

Respiratory cycle: A respiratory cycle is constituted by the inspiration followed by the expiration of a given volume of gas, called tidal volume. The duration of the respiratory cycle is the respiratory or ventilatory period, whose reciprocal is the ventilatory frequency.

Respiratory exchange ratio: See RESPIRATORY QUOTIENT.

Respiratory frequency (f_R): The number of breathing cycles per unit of time. Synonymous with breathing frequency (f_B).

Respiratory quotient (RQ, R): Quotient of the volume of CO_2 produced divided by the volume of O_2 consumed by an organism, an organ, or a tissue during a given period of time. Respiratory quotients are measured by comparing the composition of an incoming and an outgoing medium, e.g., inspired and expired gas, inspired gas and alveolar gas, or arterial and venous blood. Sometimes the phrase "respiratory exchange ratio" is used to designate the ratio of CO_2 output to the O_2 uptake by the lungs, "respiratory quotient" being restricted to the actual metabolic CO_2 output and O_2 uptake by the tissues. With this definition, respiratory quotient and respiratory exchange ratio are identical in the steady state, a condition which implies constancy of the O_2 and CO_2 stores.

Shunt: Vascular connection between circulatory pathways so that venous blood is diverted into vessels containing arterialized blood (right-to-left shunt, venous admixture) or vice versa (left-to-right shunt). Right-to-left shunt within the lung, heart, or large vessels due to malformations are more important in respiratory physiology. Flow from left to right through a shunt should be marked with a negative sign.

Specific airway conductance (SGaw): Airway conductance divided by the lung volume at which it was measured, i.e., normalized airway conductance. SGaw = Gaw/TGV.

Specific airway resistance (SRaw): Airway resistance multiplied by the volume at which it was measured. SRaw = Raw x TGV.

Spirograph: Mechanical device, including bellows or other scaled, moving part, which collects and stores gases and provides a graphical record of volume changes. See BREATHING PATTERN, RESPIRATORY CYCLE.

Spirometer: An apparatus similar to a spirograph but without recording facility.

Static lung compliance (C_{Lst}): Lung compliance measured at zero flow (breath-holding) over linear portion of the volume-pressure curve above FRC. See COMPLIANCE.

Static transpulmonary pressure (P_{st}): Transpulmonary pressure measured at a specified lung volume; e.g., P_{st}TLC is static recoil pressure measured at TLC (maximum recoil pressure).

Sulfur dioxide (SO_2): Colorless gas with pungent odor, released primarily from burning of fossil fuels, such as coal, containing sulfur.

STPD conditions (STPD): Standard temperature and pressure, dry. These are the conditions of a volume of gas at 0°C, at 760 torr, without water vapor. A STPD volume of a given gas contains a known number of moles of that gas.

Surfactant, pulmonary: Protein-phospholipid (mainly dipalmitoyl lecithin) complex which lines alveoli (and possibly small airways) and accounts for the low surface tension which makes air space (and airway) patency possible at low transpulmonary pressures.

Synergism: A relationship in which the combined action or effect of two or more components is greater than the sum of effects when the components act separately.

Thoracic gas volume (TGV): Volume of communicating and trapped gas in the lungs measured by body plethysmography at specific lung volumes. In normal subjects, TGV determined at end expiratory level corresponds to FRC.

Tidal volume (TV): That volume of air inhaled or exhaled with each breath during quiet breathing, used only to indicate a subdivision of lung volume. When tidal volume is used in gas exchange formulations, the symbol V_T should be used.

Tissue resistance (R_{ti}): Frictional resistance of the pulmonary and thoracic tissues.

Torr: A unit of pressure equal to 1,333.22 dynes/cm^2 or 1.33322 millibars. The torr is equal to the pressure required to support a column of mercury 1 mm high when the mercury is of standard density and subjected to standard acceleration. These standard conditions are met at 0°C and 45° latitude, where the acceleration of gravity is 980.6 cm/sec^2. In reading a mercury barometer at other temperatures and latitudes, corrections, which commonly exceed 2 torr, must be introduced for these terms and for the thermal expansion of the measuring scale used. The torr is synonymous with pressure unit mm Hg.

Total lung capacity (TLC): The sum of all volume compartments or the volume of air in the lungs after maximal inspiration. The method of measurement should be indicated, as with RV.

Total pulmonary resistance (R_L): Resistance measured by relating flow-dependent transpulmonary pressure to airflow at the mouth. Represents the total (frictional) resistance of the lung tissue (R_{ti}) and the airways (Raw). $R_L = R_{aw} + R_{ti}$.

Trachea: Commonly known as the windpipe; a cartilaginous air tube extending from the larynx (voice box) into the thorax (chest) where it divides into left and right branches.

Transpulmonary pressure (P_L): Pressure difference between airway opening (mouth, nares, or cannula opening) and the visceral pleural surface, in cm H_2O. Transpulmonary in the sense used includes extrapulmonary structures, e.g., trachea and extrathoracic airways. This usage has come about for want of an anatomic term which includes all of the airways and the lungs together.

Ventilation: Physiological process by which gas is renewed in the lungs. The word ventilation sometimes designates ventilatory flow rate (or ventilatory minute volume) which is the product of the tidal volume by the ventilatory frequency. Conditions are usually indicated as modifiers; i.e.,

$\dot{V}_E$ = Expired volume per minute (BTPS),
and
$\dot{V}_E$ = Inspired volume per minute (BTPS).

Ventilation is often referred to as "total ventilation" to distinguish it from "alveolar ventilation" (see VENTILATION, ALVEOLAR).

Ventilation, alveolar ($\dot{V}_A$): Physiological process by which alveolar gas is completely removed and replaced with fresh gas. Alveolar ventilation is less than total ventilation because when a tidal volume of gas leaves the alveolar spaces, the last part does not get expelled from the body but occupies the dead space, to be reinspired with the next inspiration. Thus the volume of alveolar gas actually expelled completely is equal to the tidal volume minus the volume of the dead space. This truly complete expiration volume times the ventilatory frequency constitutes the alveolar ventilation.

Ventilation, dead-space ($\dot{V}_D$): Ventilation per minute of the physiologic dead space (wasted ventilation), BTPS, defined by the following equation:

$$\dot{V}_D = \dot{V}_E(PaCO_2 - P_ECO_2)/(PaCO_2 - P_ICO_2)$$

Ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$): Ratio of the alveolar ventilation to the blood perfusion volume flow through the pulmonary parenchyma. This ratio is a fundamental determinant of the O_2 and CO_2 pressure of the alveolar gas and of the end-capillary blood. Throughout the lungs the local ventilation/perfusion ratios vary, and consequently the local alveolar gas and end-capillary blood compositions also vary.

Vital capacity (VC): The maximum volume of air exhaled from the point of maximum inspiration.